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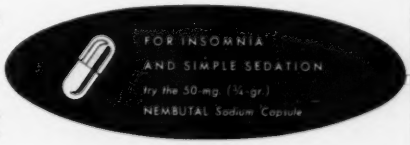

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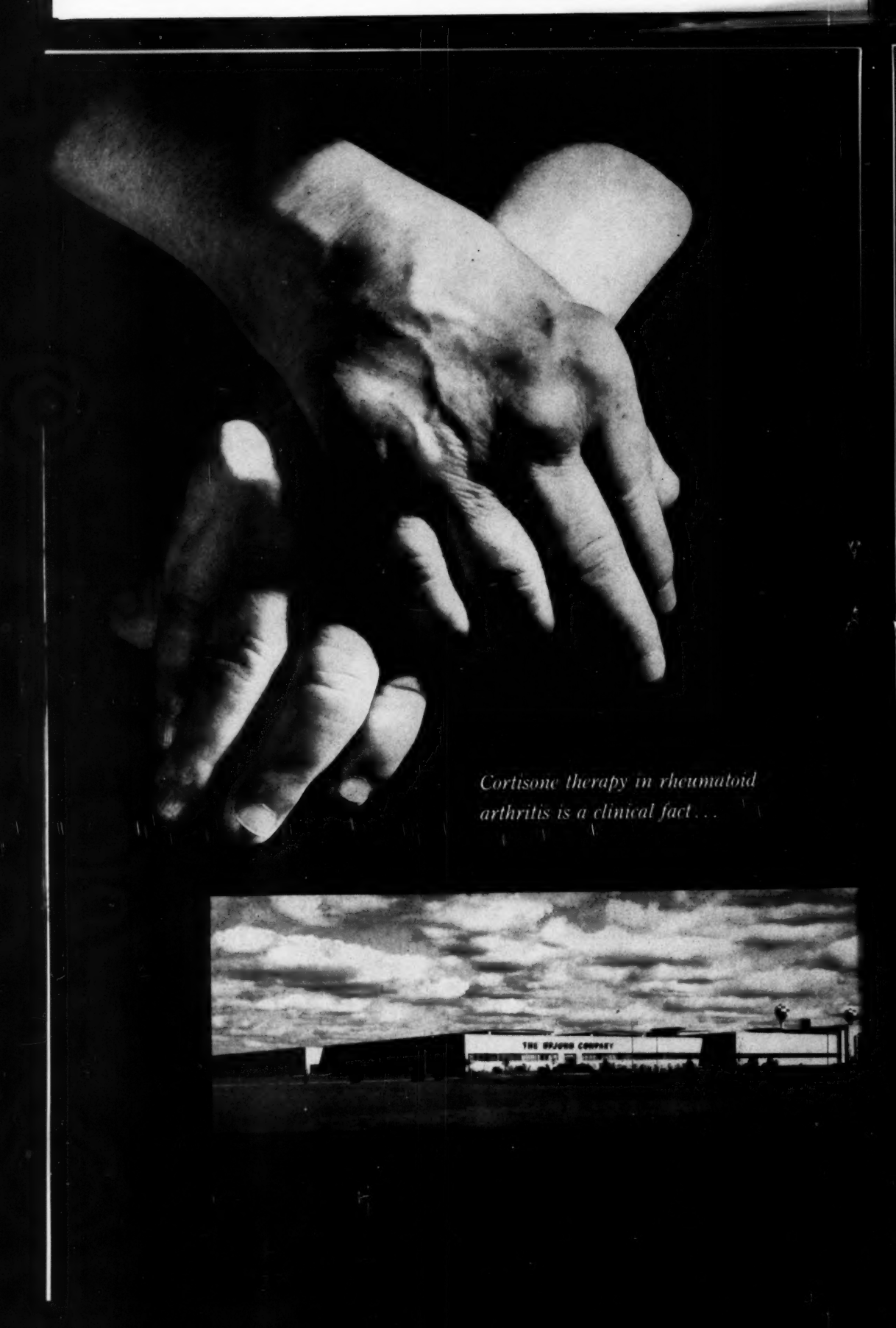
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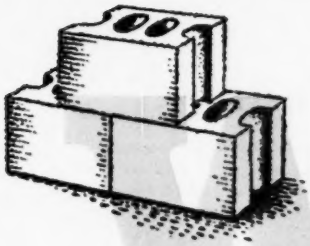

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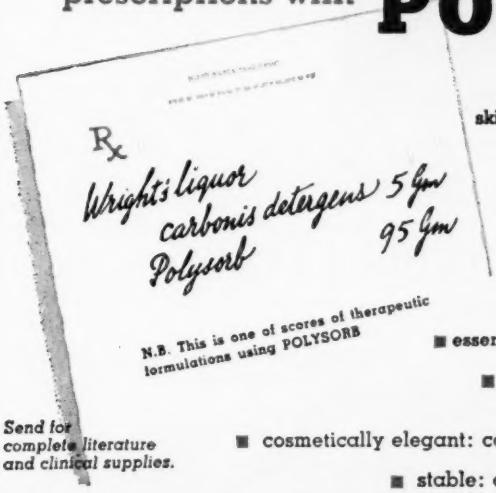
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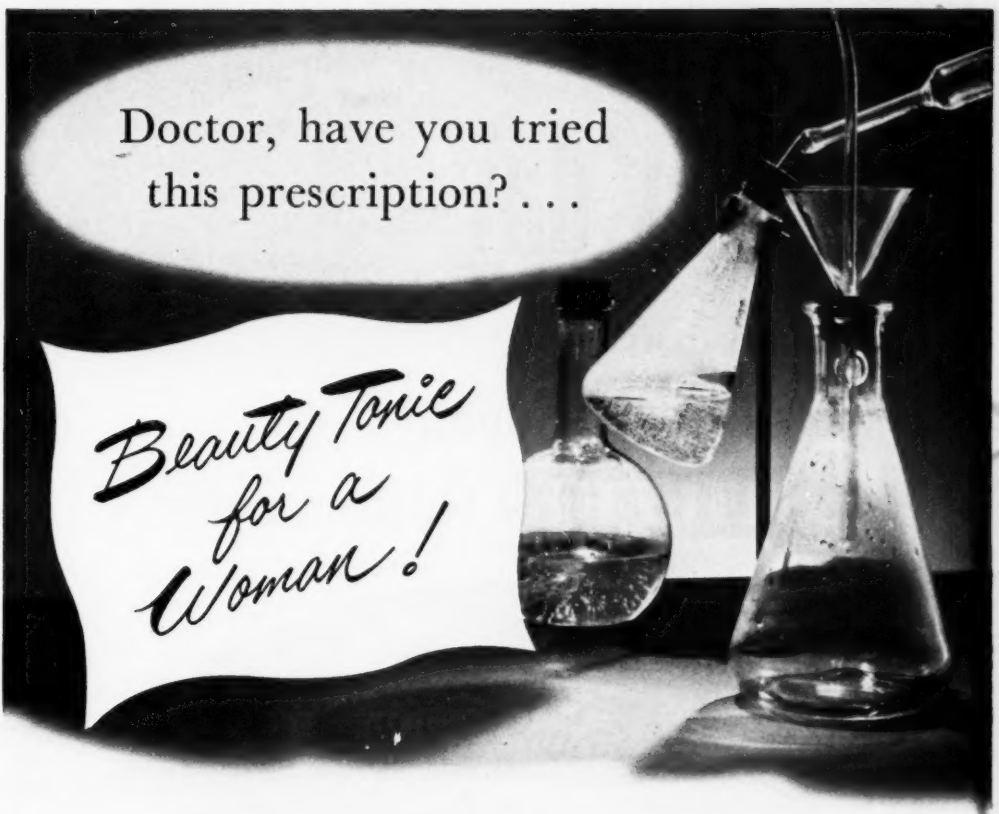

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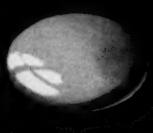

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Archives of Dermatology and Syphilology

VOLUME 66 JULY 1952 NUMBER 1

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NEUROGENIC FACTORS IN CONTACT DERMATITIS

WILLIAM B. GUY, M.D.
With the Technical Assistance of Miss Ruth Mingonet
PITTSBURGH

THE INFLUENCE of the nervous system on disease has been the subject of close attention in recent years, particularly that of the portion of the nervous system involved in emotion or the affect of the human being. Such influence has long been accepted in the so-called functional disorders, but the emotions have recently been implicated in many organic diseases as well. Peptic ulcer, rheumatoid arthritis, hypertension, obesity, and other diseases involving actual structural changes are thought to be truly psychosomatic in origin by many writers.

For years dermatologists have recognized the role of nervous and emotional factors in several common dermatoses. In 1891 Brocq and Jacquet [1] coined the term *neurodermite* for a common chronic dermatitis hitherto designated as one of the forms of eczema. Among the many observers who have since written extensively about the effect of emotional and nervous states on the skin, the Americans Stokes,[2] Michelson,[3] Becker,[4] and Lynch [5] have made outstanding contributions. Psychosomatic factors have been implicated in the causation of many dermatoses. Rosacea, pruritis ani et vulvae, dyshidrosis, chronic urticaria and angioneurotic edema, alopecia areata, and circumscribed neurodermatitis are considered primarily neurogenic by a significant number of dermatologists. Strangely enough, the allergists recognize the effect of nervous tension and fatigue on the atopic diseases, atopic eczema, asthma, and hay fever, yet many dermatologists exclude all allergic implications in atopic eczema and term it disseminated neurodermatitis.

From the Department of Dermatology and Syphilology and the Addison Gibson Laboratory, School of Medicine, University of Pittsburgh.

Read before the Section on Dermatology and Syphilology at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 13, 1951.

1. Brocq, L., and Jacquet, L., in Besnier, Brocq, L., and Jacquet, L.: La pratique dermatologique, Paris, Masson & Cie, 1902, Vol. 3, p. 141.

2. Stokes, J. H.: The Effect on the Skin of Emotional and Nervous States: Masochism and Other Sex Complexes in the Background of Neurogenous Dermatitis, Arch. Dermat. & Syph. **22**:803 (Nov) 1930.

3. Michelson, H. E.: Psychosomatic Studies in Dermatology: The Motivation of Self-Induced Eruptions, Arch. Dermat. & Syph. **51**:245 (April) 1945.

4. Becker, S. W.: Functional Medicine from the Dermatologist's Viewpoint, J. Med. **21**:526, 1941.

5. Lynch, F. W.; Hinckley, R. G., and Cowan, D. W.: Psychosomatic Studies in Dermatology: Psychobiologic Studies of Patients with Atopic Eczema (Disseminated Neurodermatitis), Arch. Dermat. & Syph. **51**:251 (April) 1945.

There are many who discount the role of psychosomatic factors in skin diseases —some who practically deny it altogether. Yet, by and large, the proponents of both views attain about the same degree of success in the management of the conditions over which they dispute. That they do suggests that many factors operate in the causation of these conditions. It is well known that environmental pressure and stress will produce an exacerbation of acne rosacea in some persons, as will ingestion of highly seasoned foods or alcoholic drinks. A circumscribed neurodermite is often seen in patients who are tried or harassed, but it also occurs frequently on the nape of the neck, together with an active seborrhea of the scalp. Skin testing and desensitization to discover allergens give gratifying results in hay fever and asthma, but not in atopic eczema, in which management by the psychosomatic approach is often so fruitful.

There is a dermatosis, seen rather frequently, over which the proponents of these two concepts differ. It is a nondescript dermatitis, sudden in onset, with a progressive course. It may be primarily vesicular, or angry erythema and edema may be prominent features at first. Later it becomes exudative. It often starts as a local process but rapidly becomes widespread, not always arranging itself symmetrically, however. The distribution may be confusing. It crosses garment borders and involves covered as well as uncovered surfaces. Yet its asymmetry leads one away from considering a toxic cause, borne by the circulating blood. The patients' discomfort and distress are salient features, and they are often out of proportion to the severity of the dermatitis. Use of the blandest of lotions and wet compresses may produce explosive exacerbations. One is literally afraid to try anything locally. We have seen many competent dematologists label this exudative neurodermatitis. Yet others, equally competent, because of its morphology will insist that it is of external origin and call it a contact dermatitis.

It has occurred to us that perhaps both sides are partially correct, that neurogenic influences as well as contactant substances may be involved. It does not seem unreasonable that prolonged mental or emotional turmoil could make the skin hyperreactive and sensitive to contactants which it ordinarily tolerates, that such sensitivity is rather broad and nonspecific, so that almost anything then touching the skin could produce a dermatitis. This concept would help to explain the peculiar distribution of the eruption we have just described, the crossing of garment borders, and the failure to confine itself to exposed areas of the skin. It also helps to explain, we believe, the pathogenesis of what many observers call acute neurodermatitis, without making clear how the nervous system can do so much to the skin.

This concept was first suggested to us when we attempted to desensitize persons with contact-type allergies by repeated patch-testing with the sensitizing substances. In some instances, when the agents were water-soluble, we were doing serial exposures with increasingly strong concentrations. In others we used the offending article itself: a piece from a garment, part of a shoe lining that had caused trouble, or perhaps nail polish. We did not feel that we succeeded in a single instance, but we did make some interesting observations. First, we found that the skin's sensitivity to contactants is extremely unstable. Reactions to a given material in the same concentration in the same person could vary from 4+ to negative and could do so within as short a period as three weeks. We concluded that unpredictable rises and falls in degree of contact sensitivity were common.

Second, we gained the impression that in some persons a heightened sensitivity could be correlated with fatigue, emotional stress, domestic tension, and other adverse conditions. In these persons, patch-test reactions would subside to degrees of less positivity or even to negativity when the subject's environmental difficulty and emotional turmoil were relieved. Admittedly these were rough observations.

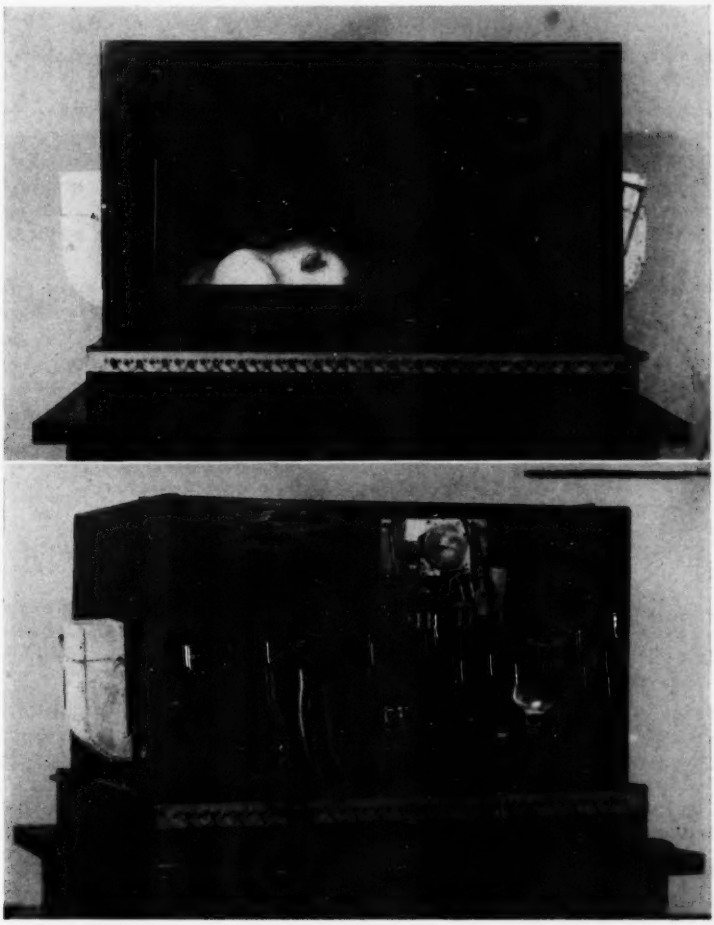

Fig. 1.—Front and back views of tension box, showing arrangement of circuit to produce combined stimuli automatically.

Patch-test reactions could be read accurately and objectively, but the patient's "emotional state" was a difficult thing to assess accurately.

Our impressions were enhanced by another fact which is common knowledge, namely, that patch tests are invalid, even possibly dangerous, when a contact dermatitis is acute and widespread, because the skin is often "reactive" then and will show

a positive response to many tested materials. We wondered whether this reactivity is not due in part to emotional agitation, irritability, and sleeplessness induced by the dermatitis itself. At least we have seen this varied, polyvalent sensitivity narrow down to one or two test materials when the dermatitis subsides, the pruritus is relieved by successful local measures, and the patient gets a few nights' sleep with adequate sedation.

INVESTIGATIVE PROCEDURE

With these rough observations on human beings as a basis, we attempted to study the matter more accurately and objectively in animals.

We chose for this study male white albino guinea pigs. We sensitized them to 2, 4-dinitrochlorobenzene according to a method developed by Landsteiner.[6] The technique was briefly as follows:

The animals were initially exposed to a 1% alcoholic solution of 2, 4-dinitrochlorobenzene applied with a glass rod to the closely depilated skin of the abdomen. The exposed areas were observed in 48 and again in 72 hours. Only an occasional animal showed a positive reaction to this initial application.

After this, a series of eight sensitizing exposures was applied, consisting of applications every other day of a 3% alcoholic solution of the material to those animals which had originally shown

TABLE 1.—*Schedule of Noise-Shock Stimuli Which Produced Maximum Disturbance of Animals**

Schedule	Noise-Shock Stimuli
1st 24 hr.	Shock and noise simultaneously
2d 24 hr.	Noise preceding shock by 1 sec.
3d 24 hr.	Noise preceding shock by 2 sec.
4th 24 hr.	Noise preceding shock by 3 sec.
5th 24 hr.	Noise preceding shock by 4 sec.

* Combined stimuli were given every 15 minutes for five days with increasing time intervals between noise and shock.

a negative reaction. After an incubation period of four weeks, the weaker 1% solution was applied again. Those animals showing a positive skin reaction to this subsequent exposure were considered sensitized to the test materials. We sensitized more than half the animals we subjected to this procedure.

We then wanted to upset these animals emotionally, to interfere with their sleep cycle, in effect, to produce a condition analogous to an anxiety state in human beings. Dr. Robert Patton, an animal psychologist of the Department of Psychology of the University of Pittsburgh, suggested the use of a tension box. This was a glass-enclosed cage, the floor of which was an electric grid capable of delivering a momentary shock to the enclosed animals. The shock was a condenser discharge, operated by relays, the condensers being of 50 microfarads value, charged with 130 volts, direct current.

The circuit had an automatic timer set to deliver the shock every 15 minutes. An element of conditioning was introduced by accompanying the shock with the noise of a loud buzzer, occurring simultaneously at first, then preceding the shock by lengthening time intervals. This was done with the idea of introducing apprehension and anxiety into the repeated mild punishment. We found that by the schedule shown in Table 1 we could make the animals restless and hyperkinetic, decrease their food and water intake, and produce weight loss.

The animals were kept in the tension box five days, the noise and shock being given every 15 minutes around the clock.

6. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds, J. Exper. Med. **61**:643, 1935.

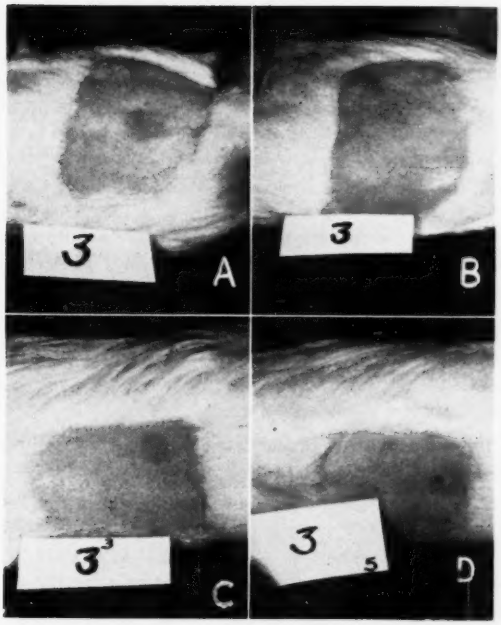

Fig. 2.—Patch-test reaction to 1% 2, 4-dinitrochlorobenzene in Animal 3. *A*, *B*, and *C* show reaction of animal under normal laboratory conditions to tests given consecutively at weekly intervals. *D* is reaction to patch test applied while animal was in tension box.

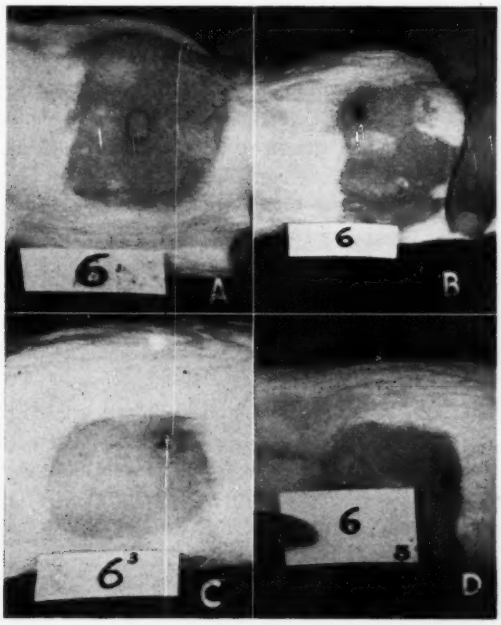

Fig. 3.—Patch-test reaction to 2, 4-dinitrochlorobenzene in Animal 6. *A*, *B*, and *C* show reactions of animal under normal laboratory conditions to tests given consecutively at weekly intervals. *D* is reaction to patch test applied while animal was in tension box.

We proceeded to subject some of the sensitized animals to this situation. We had to use those in which reactions had been relatively mild, so that, if the tension period produced any difference in their degree of sensitivity, it would be apparent quantitatively. Also, we chose only those which had previously shown relative stability of reaction to repeated patch tests; comparable response to three consecutive weekly tests was considered satisfactory.

Five animals satisfied these requirements and were placed in the tension box for five days. At the end of the third 24 hours, a patch test of 1% 2, 4-dinitrochlorobenzene was applied; 48 hours later, at the end of the five-day tension period, the patch tests were read. All these animals showed a tendency to increased reactivity.

As a control measure, we subjected 10 other animals which had not been sensitized to 2, 4-dinitrochlorobenzene to the five-day period in the tension box. At the end of 72 hours we applied patch tests with a 1% alcoholic solution of the material and read them at the end of the five-day period. Only one of these animals showed a positive response.

COMMENT

We felt that this investigation on laboratory animals was the first step in confirming our impression that emotional factors influence the sensitivity of the skin to contactants. Whether anxiety and emotional stress such as human beings display

TABLE 2.—*Reactions of Five "Stable Reactors"**

	Exposure			
Animal	1st	2d	3d	4th
1.	++	+	+	+++
3.	++	++	++	+++
5.	++	+	+	+++
6.	++	++	+++	++++
8.	+	+	+	++

* First, second, and third exposures were under normal laboratory conditions. Fourth exposure was while animal was in tension box.

can be produced in a phlegmatic animal like the guinea pig is open to question. At least we felt that the method chosen to disturb them could not alter their skin function in any other way. The degree to which we upset them could be determined only by their overt behavior. After their period in the tension box, they were not the immobile, passive, "poker-faced" animals that guinea pigs usually are. They moved about a great deal, after the warning noise and shock particularly. Their intake of food and water decreased; they all lost weight, some more than 100 gm., and they were difficult to handle, biting and scratching while being clipped and depilated.

We anticipated theoretical objections to the patch-testing technique also. In painting an alcoholic solution on the skin and leaving it uncovered, the end-result was the pure crystalline test material left dry on the skin surface in a few minutes. But the quantitative difference in reaction to a 1% solution and a 3% solution in any sensitized animal was sufficient to dispel that objection in our minds.

An investigation on human subjects is needed to verify our proposition. But the difficulty involved in producing measurable emotional turmoil, anxiety, or apprehension under experimental conditions in human subjects seems most difficult and complex.

SUMMARY AND CONCLUSIONS

A great many factors are accepted as having a bearing on or predisposing to contact dermatitis. A blond or a dry senile skin is usually more susceptible. The thickness of the cornified epithelial layer, the presence or absence of a protective coat of sebum, and a seborrheic diathesis have all been discussed as influencing the skin's sensitivity to contactants. Environmental conditions, such as heat, friction, moisture, and exposure to organic solvents and keratolytic chemicals, are known to be predisposing factors.

The influence of the nervous system in contact dermatitis has been overlooked, we believe. This seems strange in view of the close embryologic association between the nervous system and the epidermis, which is thought to be the shock organ in contact sensitivity.

This investigation indicates that disturbing guinea pigs, interfering with their sleep cycle, and distracting them to the point of decreasing their food intake and making them lose weight increases the sensitivity of their skin to contactants. We infer from this that similar environmental influences, involving infinitely more complex mechanisms and channels, could do the same thing in human beings; that sometimes a contact dermatitis is also a neurodermatitis, and, conversely, that the trigger factor in a neurodermatitis can be one or many contactants.

ABSTRACT OF DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul: Some may question the author's choice of the word "neurogenic" in the title, but little is to be gained by arguing that point. The paper offers two principal fields for consideration, and I shall first discuss the experimental aspects. Briefly, animals were sensitized by chemical contact, thrown into an anxiety state, retested, and thus demonstrated to have developed increased reactivity. I believe the results of the study are valid, but I must call attention to several possible defects in the experimental procedure: the small number of animals, the lack of measurement of the quantity (in addition to the concentration) of dye employed, and the neglect of the possible effect of repeated testing without use of the tension box. These criticisms merely point out that more remains to be done and that the study opens several additional vistas which should be investigated. I believe that further investigation in the experimental field will confirm Dr. Guy's findings. Under the direction of Dr. Ralph Rossen, Commissioner of Mental Health in Minnesota's Division of Public Institutions, two clinical dermatologists are at work hoping to investigate reactions to intracutaneous tests on disturbed patients during and after shock therapy.

Properly, the main emphasis of Dr. Guy's paper is clinical. He has observed eruptions having features of both atopic dermatitis (neurodermatitis) and contact dermatitis, and he surmises that "emotional turmoil could make the skin hyperactive and sensitive to contactants which it ordinarily tolerated." This impression was supported by his observation of unpredictable variation in reactions to series of patch tests. Dr. Guy calls attention to the difficulty in assessing such emotional factors, but many of us will agree with him that such difficulty must not lead to ignoring these factors. I have long been convinced of their presence and importance. There is general acceptance of the observation that atopic dermatitis (neurodermatitis) often appears on sites exposed to irritants or sensitizers, but there are differences of opinion on whether these events represent contact dermatitis transforming to atopic dermatitis or merely precipitation of atopic dermatitis by the contactants (as they can certainly aggravate it). "Diaper dermatitis" often transforms to atopic dermatitis of greater or different extent. Dyshidrosiform and nummular dermatitides are often aggravated by contactants and may also merge with more characteristic forms of atopic dermatitis. On what day does one disease become the other? Such an argument is probably futile. This is not the time, nor have I the inclination, to discuss the rather obviously

important application of these studies and views as they relate to occupational dermatitis. It is somewhat surprising that employers and insurers have not given substantial support to further investigations in this field.

It is my opinion that when contact dermatitis takes on clinical features of atopic dermatitis one can rarely, if ever, demonstrate significant allergic reactivity by the application of intracutaneous tests, a method of study disclaimed by only a few allergists and widely applied in practice by allergists and other practitioners for allergic (and too often for nonallergic) disorders. On the other hand, these patients do show the emotional characteristics so constantly seen in atopic dermatitis (neurodermatitis), and I believe these features can be of pathogenetic, though not necessarily primary, importance and are not psychologic changes occurring entirely as a result of the eruption.

If Dr. Guy's clinical and experimental observations are valid, and I believe that they are, they reemphasize a need for viewing all eczema as one problem, not divisible into forms which can be sharply set apart, but rather with very considerable overlapping among the contact, atopic, infectious, and seborrheic forms and possibly even some of those due to drugs. Dr. Guy is to be sincerely thanked for a presentation that again points out the need for attention to multiple precipitating and aggravating factors in illness and, more specifically and clearly, in contact dermatitis. He is to be congratulated for his willingness to express in a controversial field the views based on his clinical observations, and also for his attempt to set up and carry out an experimental study to determine a justification for his views.

TINEA CAPITIS IN THE ADULT AND ADOLESCENT

JAMES LEWIS PIPKIN, M.D.
SAN ANTONIO, TEXAS

MY EXPERIENCE, as well as a geographic survey of the United States, indicates that the incidence of tinea capitis in the postpuberal person is higher than is generally realized. The physicians' index of suspicion regarding the possibility of tinea capitis in the adult has been lowered over the years by the medical literature emphasizing the rarity of this entity. This impression of rarity is partly due to the regional geographic distribution of the fungi capable of producing postpuberal tinea capitis, because of which dermatologists in some parts of the country very rarely see such patients. However, the ever-shifting incidence of such fungi, both locally and nationally, makes it important for the physicians in all sections of the country to appreciate the possibility of this clinical entity after puberty.

In 1925, Fox and Fowlkes [1] reviewed the world literature on ringworm of the scalp in the adult, surveying 50 cases and reporting 3 of their own. Eighteen [2] additional isolated cases (excluding those of favus) have been reported in the United States since that time.

Tinea capitis in the adult is commoner in Europe, China, and Japan than in the United States. From 1927 to 1935, Maschkilleisson [3] observed in Moscow and

Read before the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23 to 26, 1951.

1. Fox, H., and Fowlkes, R. W.: Ringworm of the Scalp in Adults, Arch. Dermat. & Syph. **11**:466 (April) 1925.

2. (*a*) Pernet, G.: Ringworm of the Scalp: Report of Case in Adult, Arch. Dermat. & Syph. **12**:267 (Aug.) 1925. (*b*) Fox, H.: Ringworm of the Scalp in the Adult: Report of Case of Kerion Due to Microsporon Audouini, ibid. **13**:398 (March) 1926. (*c*) Chambers, S. O.: Ringworm of the Scalp Occurring in an Adult, ibid. **13**:447 (March) 1926. (*d*) Bechet, P. E.: Tinea Tonsurans in an Adult, ibid. **13**:710 (May) 1926. (*e*) Andrews, G. C.: Kerion Celsi: Lichen Trichophyticum, ibid. **16**:477 (Oct.) 1927. (*f*) White, C.: Ringworm of the Scalp in Adults, Illinois M. J. **56**:152 (Aug.) 1929. (*g*) Cummer, C. L.: Tinea Capitis with Kerion in an Adult Caused by Trichophyton Gypseum—Lacticolor, Arch. Dermat. & Syph. **36**:844 (Oct.) 1937. (*h*) Mendelsohn, H. V., and Muskatblitt, E.: Tinea Capitis in an Adult, New York J Med. **38**:803 (May 15) 1938. (*i*) Benson, J. A.: Kerion Celsi of the Scalp in an Adult, Arch. Dermat. & Syph. **39**:434 (March) 1939. (*j*) Mitchell, J. H.: Epidemic Ringworm of the Scalp, M. Clin. North America **32**:283 (Jan.) 1948. (*k*) Andrews, G. C.: Case Report, Arch. Dermat. & Syph. **57**:506 (March) 1948. (*l*) Lewis, G. M.: Tinea Capitis in an Adult, ibid. **57**:506 (March) 1948. (*m*) Morgan, D. B.: Report of a Case of Ringworm of the Scalp in an Adult, J. Kansas M. Soc. **50**:231 (May) 1949. (*n*) Hirschmann, V. R., and Olansky, S.: Ringworm of the Scalp in an Adult, Arch. Dermat. & Syph. **61**:122 (Jan.) 1950. (*o*) Greenhouse, J. M.: Trichophyton Violaceum Infection of Scalp and Glabrous Skin of an Adult, A. M. A. Arch. Dermat. & Syph. **63**:503 (April) 1951. (*p*) Kligman, A. M., and Constant, E. R.: Family Epidemic of Tinea Capitis Due to Trichophyton Tonsurans (Variety Sulfureum), ibid. **63**:493 (April) 1951. (*q*) Wilson, J. W.: Tinea Capitis (Microsporum Lanosum) in a Woman Aged 72, ibid. **63**:403 (March) 1951.

3. Maschkilleisson, L. N.: Zur Frage über Trichophytia superficialis capillitii adultorum, Dermat. Wchnschr. **102**:765 (June 13) 1936.

Voronezh 53 cases of superficial Trichophyton infections of the scalp in persons over 18 years of age. He collected up to the year 1934 in the world literature (excluding Japanese reports) 606 cases of superficial Trichophyton and Microsporum infections of the scalp in adults (persons over 16 years of age). In 1931, Chen and Kurotchkin [4] reported 21 microscopically and culturally proved cases from China. In Japan, from 1901 to 1910, Mine and Orimo [5] observed 120 persons (between 16 and 60 years of age) with tinea capitis, 63 of these being adults (over 21 years of age).

GEOGRAPHIC SURVEY

A geographic survey, spot-checking the United States, was made by a questionnaire to dermatologists. Their response was gratifying, as I received 106 replies to the 125 inquiries.

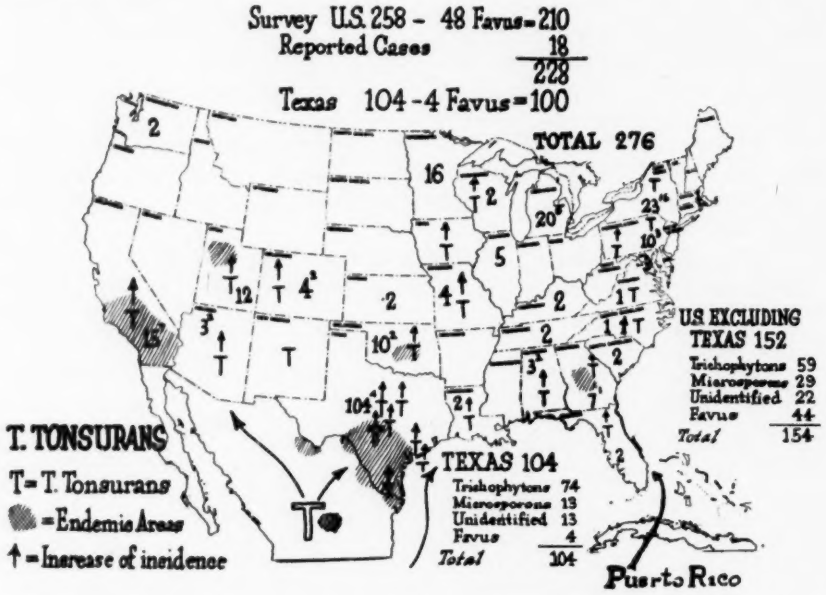

Fig. 1.—Tinea capitis in adults in the United States. Large figures indicate number of cases of tinea capitis in adults; small figures, number of cases of favus in adults.

Fifty-six reported that they had observed a total of 258 cases of ringworm infection in the scalp of adults, as shown on the map (Fig. 1). The large figures indicate the total number of tinea capitis cases in adults in each state, and the small figures denote the favus cases.

4. Chen, F. K., and Kurotchkin, T. J.: Tinea of Scalp Among Adults in Peiping, Nat. M. J. China **17**:185 (April) 1931.

5. Mine, M., and Orimo, T.: Statistische Studie der parasitären Hautkrankheiten in der dermatologischen Universitäts Klinik zu Tokyo, Jap. Ztschr. Dermat. u. Urol. **10**:457 (June) 1910.

Since the tonsurans (crateriforme) species group of Trichophyton was so frequently encountered in the present series, occurring in 42 instances (73%), 29 times in 39 adult scalps (75%) and 13 times in 18 adolescents (72%), I felt that a report showing the geographic distribution of this organism (as shown on the map by the letter *T*) would probably indicate where tinea capitis in the adult should be found. This survey revealed that the Trichophyton tonsurans (crateriforme) species group is widely distributed over the southern half of the United States from coast to coast. Certain endemic foci (note shading on map) were particularly observed in Texas, Oklahoma, California, Utah, and Georgia, reaching almost epidemic proportions in Texas and southern California. Whether or not scalp infections caused by this group of organisms are on the increase is also of interest. The small arrows on the map indicate the areas where a definite increase in the incidence of scalp infections caused by this organism appears. However, this apparent increase is difficult to evaluate, since it may merely be due to more accurate diagnosis and more precise classification.

The high incidence in southwestern United States and southern California of Trichophyton infections, the majority being due to the tonsurans species group, is probably a result of the spread from Mexico and Central America. For a number of years my associates and I have noticed that the trichophytoses represented a large percentage of the scalp infections originating in northern Mexico and that infection due to the tonsurans (crateriforme) group made up a very high percentage of these. A number of endemic foci of T. tonsurans have been noted along the border of Mexico, as indicated by shading on the map in Figure 1. Also, many patients have been observed over the years with scalp infections due to the tonsurans group originating in Monterey, Mexico. Gonzalez Ochoa and Romo Vasquez,[6] from Mexico City, Mexico, reported that 92% of their cases of tinea capitis were due to T. tonsurans. The high incidence over the southern states can possibly be explained by the infection spreading from Central America and Puerto Rico. Carrion and Silva,[7] of Puerto Rico, reported that 42.8% of the tinea capitis infections in their series was caused by the T. tonsurans group.

In answering the inquiry, Dr. J. Walter Wilson,[8] of Los Angeles, reported that he had observed a number of cases of tinea capitis due to this organism. Dr. Harold Price,[8] also of Los Angeles, has observed nearly 100 children infected with T. tonsurans. He stated that 12% of the scalp infections observed by him were due to this organism. Dr. W. S. Morginson,[8] of Salt Lake City, has observed 10 cases in adults due to the tonsurans group. In other areas there has been a definite increase of infections due to this organism, as reported in Oklahoma City, by Dr. John Lamb[8]; in Madison, Wis., by Dr. Sture A. M. Johnson[8]; in Iowa City, by Dr. Ruben Nomland,[8] and in Pittsburgh, by Dr. W. B. Guy.[8] Since adults are susceptible to this organism, a careful search should reveal more adult infections in these endemic and epidemic areas.

In regard to whether tinea capitis in the adult presented a different clinical picture from that commonly seen in children, the answer was affirmative in 30 of the

6. Gonzalez Ochoa, A., and Romo Vasquez, B.: Dermatofitos causantes de tina de la piel cabelluda en la ciudad de Mexico, Rev. Inst. salub. y enferm. trop. **6**:145, 1945.

7. Carrion, A. L., and Silva, M.: Ringworm of the Scalp in Puerto Rico, Puerto Rico J. Pub. Health **19**:329 (March) 1944.

8. Personal communication to the author.

TABLE 1.—*Data on Cases of Tinea Capitis in Adults* *

Case No.	Year	Race	Sex	Age	Age at Onset	Duration	Menstrual History	Type of Lesion	Involvement of Skin	Involvement of Nails	Source of Infection	Wood Light	Microscopic Examination	Culture	Treatment	Outcome	Time Observed After Cure
1	1931	AA	F	36	36	6 mo.	M	Patchy hair loss; folliculitis; stubs	None	None	Son	Not available	+ large spores in chains	T. tonsurans var.?	Roentgen epilation	Cured	1 yr.
2	1931	AA	F	35	35	1 mo.	M	One scaly patch with stubs	None	None	Daughter	Not available	+ small spores	M. lanosum	Topical	Cured in 4 wk.	20 yr.
3	1932	AA	F	50	45	5 yr.	M	Scaly patch with stubs; black dot	None	None	Unknown	Not available	+ large spores; endothrix	T. tonsurans var. crateriforme	Roentgen epilation	Cured	19 yr.
4	1935	AA	F	30	30	6 mo.	M	One scaly patch with stubs	None	None	Daughter	+	+ small spores	M. lanosum	Topical	Cured in 6 wk.	3 mo.
5	1937	LA	F	36	26	10 yr.	M	Black dot	Shoulder	3 nails	Unknown	—	+ large spores; endothrix	T. tonsurans var. acuminatum	Topical	Lost	1 visit
6	1940	LA	F	35	6-7	20 yr.	Unk.	Extensive black dot	None	None	Unknown	—	+ packed with spores; endothrix	T. violaceum	Topical	Lost	.....
7	1942	LA	F	31	27	4 yr.	H	Folliculitis with stubs	None	6 nails	Beauty parlor	—	+ large spores in chains; endothrix	T. tonsurans var. sulfureum	Roentgen epilation	Cured	9 yr.
8	1942	LA	F	24	24	8 wk.	M	Subacutely inflamed plaque with stubs; L. E.-like (early) inflamed semikerion	None	None	Child, kerion	—	+ large spores in chains; endothrix	T. tonsurans var. crateriforme	Topical	Cured; Formula No. 2	1½ yr.
9	1943	AA	F	42	38	4 yr.	H	Minimum hair loss; few stubs and dots	Neck, shoulders	None	Maid (nails)	+ lusterless gray in gray hair	+ large spores in chains; endothrix	T. tonsurans var. sulfureum	Roentgen epilation	Cured	7 yr.
10	1943	AA	F	62	62	3 mo.	0	Loss of hair; stubs	Face, eyebrows, lashes	None	Kitten	+ bright	+ small spores	M. lanosum	Topical	Cured in 4 wk.	7 yr.
11	1944	AA	F	22	19	3 yr.	M	Two patches 1 cm.; multiple small areas with stubs	Neck, shoulders, hand	10 nails	Beauty parlor (nails)	—	+ large spores in chains; endothrix	T. tonsurans var. crateriforme	Roentgen epilation	Cured	7 yr.
12	1944	AA	F	32	32	2 mo.	M	Small patchy hair loss with short stubs	None	None	Unknown	—	+ large spores in chains; endothrix	T. tonsurans var.?	Topical	Lost	.....
13	1944	LA	F	28	7	21 yr.	M	Small patches of alopecia; mild folliculitis with stubs	None	None	Unknown	—	+ large spores, endothrix square, in chains	T. tonsurans var. crateriforme	Roentgen epilation	Cured	6 yr.
14	1945	AA	F	25	13	12 yr.	M	Patchy loss of hair with stubs and few dots	Body, hand	1 nail	Unknown	—	+ large spores in chains, square endothrix	T. tonsurans var. crateriforme	Roentgen epilation	Cured	6 yr.
15	1945	AA	F	27	15	12 yr.	M	3 small 0.5-cm. areas of alopecia with stubs	Neck, shoulders, lashes, brows	None	Mother (Case 16)	—	+ large spores; endothrix	T. tonsurans var. sulfureum	Roentgen epilation	Cured	6 yr.

16	1945	AA	F	63	7-8	55 yr.	0	Very few stubs; asymptomatic	Neck, shoulders	None	School	+ dead white in gray hair	+ large spores; endothrix	T. tonsurans var. sulfureum	No treatment	60 yr. duration; no change	6 yr.
17	1945	AA	F	20	6	20 yr.	M	Extensive black dot with marked loss of hair; curled hair	Neck, face, buttocks	Nails	School	—	+ packed medium-sized square spores; endothrix	T. tonsurans var. sulfureum	Epilated at 7 yr. of age	Failed	Age 26, still infected
18	1946	LA	F	27	26	Few mo.	M	Angulated patches with stubs, pustules, and furuncles	Neck	None	Beauty parlor	—	+ large spores, endothrix square, in chains	T. tonsurans	Topical; Formula No. 2	Cured in 9 mo.	5 yr.
19	1946	N	F	39	39	3 mo.	H	Gray patch with stubs	None	None	Child	+ dull green	+ small spores	M. audouini	Topical	Cured in 3 mo.	2 yr.
20	1946	AA	F	68	68	2 mo.	0	Generalized loss of hair with stubs	Face, neck, eyebrows	None	Kitten	+ bright golden	+ small spores	M. lanosum	Topical	Cured in 5 wk.	5 yr.
21	1946	LA	F	34	6-7	28 yr.	M	L. E.-like (late) extensive alopecia with stubs and dots, pustules, scarring, and atrophy	Neck	None	Unknown	—	+ large spores; square, packed endothrix	T. tonsurans var. sulfureum	Topical	No change in 4 yr.	4 yr. still infected
22	1947	AA	F	47	45	2 yr.	H	Perifollicular erythema; mild folliculitis with stubs and dots	Shoulder, neck	None	Unknown	—	+ large spores; endothrix packed	T. tonsurans var. sulfureum	Topical, 4 yr.	No change	4 yr.
23	1947	LA	F	22	18	4 yr.	M	Mild folliculitis; broken-off hair stubs; black dot	None	None	Sisters	—	+ endothrix packed in shaft; square spores	T. tonsurans var. sulfureum	Refused treatment	No change	4 yr.
24	1947	LA	F	26	20	6 yr.	M	Mild folliculitis; broken-off hair stubs; black dot	Nape	2 nails	Sisters	—	+ endothrix packed in shaft; square spores	T. tonsurans var. sulfureum	Refused treatment	No change	4 yr.
25	1947	LA	F	20	15	5 yr.	M	Mild folliculitis; broken-off hair stubs; black dot	None	1 nail	Sisters	—	+ endothrix packed in shaft; square spores	T. tonsurans var. sulfureum	Refused treatment	No change	4 yr.
26	1948	LA	F	34	30	4 yr.	M	Extensive black dot	None	None	Unknown	—	+ large spores; endothrix; hair packed	T. violaceum	Refused epilation; topical treatment 8 mo.	No change	Lost
27	1949	AA	F	56	6 (?)	50 yr. (?)	0	Stubs, black dots throughout long hair	Nape, face, shoulders	None	Unknown	—	+ endothrix chains	T. tonsurans var. sulfureum	Roentgen epilation Second time	Failed Cured	1 yr. 2 yr.
28	1949	AA	F	79	79	2 mo.	0	Noninflammatory generalized thinning; stubs	Face, neck, chest, back	None	Kitten	+ bright yellow	+ small spores	M. lanosum	Topical	Cured in 1½ mo.	2 yr.
29	1949	LA	F	21	21	2 mo.	M	Few scattered areas of folliculitis and furuncle with stub in center	None	None	Niece	—	+ large spores square, in chains	T. tonsurans var. crateriforme	Topical Formula No. 1, phenol	Cured in 9 mo.	2 yr.

TABLE 1.—*Data on Cases of Tinea Capitis in Adults**—Continued

Case No.	Year	Race	Sex	Age	Age at Onset	Duration	Menstrual History	Type of Lesion	Involvement of: Skin	Involvement of: Nails	Source of Infection	Wood Light	Microscopic Examination	Culture	Treatment	Outcome	Time Observed After Cure
30	1949	LA	F	67	67	10 days	0	Pustules with stubs; few dots	Nape	None	Grandchild	—	+ large spores square, in chains	T. tonsurans var. crateriforme	Topical, Formula No. 1, phenol	Cured in 2 mo.	2 yr.
31	1949	AA	F	36	36	5 mo.	M	Folliculitis; furunculosis with canalizing sinuses; very short stubs	None	None	Children	—	+ large spores square, in chains	T. tonsurans var. crateriforme	Topical, Formula No. 2	Cured in 5 mo.	1 yr.
32	1950	LA	F	65	50	15 yr.	0	Irregular loss of hair; perifollicular erythema with mild folliculitis, stubs, and dots scattered through long normal hair	Neck, chest, back, arm, hands finger	None	Beauty parlor?	+ lusterless gray in gray hair	+ large spores endothrix	T. tonsurans var. sulfureum	Topical	No improvement; under treatment	.....
33	1950	LA	F	45	30	15 yr.	M	Few scattered short stubs under scales; mild folliculitis; black dot	None	None	Unknown	+ dull white in gray hair	+ large spores square, in chains	T. tonsurans var. sulfureum	Topical	Under treatment	.....
34	1950	AA	F	45	45	6 wk.	0	1 bald patch, smooth in center; alopecia areata-like stubs at edge	Shoulder	None	Niece or cat	+ bright yellow	+ small spores	M. lanosum	Topical	Cured in 6 wk.	8 mo.
35	1950	AA	F	60	58	2 yr.	0	Linear hair loss, noninflammatory with stubs interspersed through long hair	Neck, face, arms	None	Unknown	+ dull white in gray hair	+ endothrix; medium-sized spores	T. tonsurans var. sulfureum	Topical	Under treatment; no change	.....
36	1950	AA	F	70	67	3 yr.	0	Generalized loss of hair, mild folliculitis with stubs surrounding erythema with stubs, few dots	Chest, neck, shoulder	None	Beauty parlor?	+ dull white in gray hair	+ large spores in chains	T. tonsurans var. sulfureum	Topical	Under treatment; no change	.....
37	1950	AA	M	62	62	3 mo.	..	Kerion with multiple sinuses; boggy granuloma with stub at rim	Face, neck	None	Horse; calves	—	+ ectothrix	T. mentagrophytes	Topical, saturated solution potassium iodide	Cured in 2 mo.	9 mo.
38	1951	LA	F	20	20	8 mo.	M	Canalizing, draining sinuses throughout boggy granuloma; stub at border	Arm	1 nail	Unknown	—	+ large spores square, in chains	T. tonsurans var. sulfureum	Topical	Cured	2 mo.
39	1951	LA	M	36	29	7 yr.	..	Large irregular angulated bald patch; cicatrizing, scarring atrophy and folliculitis with stubs under crusts at border	None	None	Unknown	—	+ endothrix; large square spores in chains	T. tonsurans var.?	Topical	Under treatment	.....

* AA means Anglo-American; LA, Latin-American, and N, Negro. Letter M denotes patient is menstruating regularly; 0, is not menstruating, and H, had hysterectomy. Formula No. 1 is anthralin ointment. Formula No. 2 is a mixture of 3% salicylic acid, 5% ammoniated mercury, and 10% precipitated sulfur.

TABLE 2.—*Data on Cases of Tinea Capitis in Adolescents*

Case No.	Year	Race	Sex	Age	Age at Onset	Duration	Menstrual History	Type of Lesion	Involvement of: Glabrous Skin	Involvement of: Nails	Source of Infection	Wood Light	Microscopic Examination	Culture	Treatment	Outcome	Period of Observation
I	1934	AA	F	15	15	3 mo.	M	1 boggy inflamed kerion	Chin	None	Unknown	Not available	+ endothrix	T. tonsurans var.?	Topical	Cured in 4 mo.	2 yr.
II	1936	AA	F	16	7	9 yr.	M	Stubs throughout long hair; minimal loss; small patches noninflammatory	Neck	1 nail	Unknown	+ dull white in blonde hair	+ endothrix in large spores in long chains	T. tonsurans var. crateriforme	Roentgen epilation	Cured	14 yr.
III	1937	LA	F	14	4	10 yr.	M	Extensive black dot with few pustules	None	1 nail	Unknown	—	+ large spores packed in stubs	T. violaceum	Roentgen epilation	Cured	13 yr.
IV	1939	LA	F	18	7	11 yr.	M	Scattered stubs through long hair with black dots	Neck, shoulder	2 nails	Unknown	—	+ endothrix, large spores in chains	T. tonsurans var. crateriforme	Topical	Lost	.....
V	1942	AA	M	13	13	3 wk.	..	2 scaly partly bald patches with stubs	Forehead, chin	None	Cat	+ bright yellow	+ small spores	M. lanosum	Topical	Cured in 6 wk.	4 yr.
VI	1944	AA	F	18	18	8 mo.	M	Furunculosis and folliculitis; later hair loss with 1-cm. partly bald patches	None	None	Unknown	+ dull gray in blonde hair	+ large spores square, in chains	T. tonsurans var. crateriforme	Roentgen epilation	Cured	6 yr.
VII	1945	LA	F	17	17	1 mo.	M	Small diffuse partly bald areas with stubs; folliculitis and furunculoid	None	None	Unknown	—	+ large spores, endothrix	T. tonsurans var. crateriforme	Topical, Formula No. 2	Cured	13 mo.
VIII	1945	LA	F	15	10	5 yr.	M	Scattered small areas with folliculitis with stubs and dots	Arms, Face, neck	None	Unknown	—	+ large spores in chains	T. tonsurans var. sulfureum	Topical	No improvement in 3 mo.; lost	.....
IX	1946	AA	F	15	15	4 mo.	M	6-cm. scaly patch with stubs interspersed through long hair	Neck	None	Band of cap	+ dull white in blonde hair	+ endothrix	T. tonsuranse var. sulfureum	Roentgen epilation	Cured	2 yr.
X	1946	AA	M	17	17	1½ mo.	..	Kerion 3 cm. in diameter with broken hair and pus	None	None	Cattle?	—	+ ectothrix	T. mentagrophytes	Topical	Cured in 7 wk.	5 yr.
XI	1947	LA	F	16	16	2 mo.	M	Thinning and patchy loss of hair with stubs; noninflammatory	None	None	Cat	+ bright yellow	+ small spores	M. lanosum	Topical	Cured in 2 mo.	2 yr.
XII	1947	LA	F	19	18	1 yr.	Unk?	Scattered folliculitis and furunculosis with stubs	None	None	Sister?	—	+ endothrix	T. tonsurans var. epilans	Topical	Lost	.....
XIII	1948	LA	M	14	14	1 mo.	..	Stubs; scaly; minimal hair loss; noninflammatory; black dots	Neck, chest, shoulder	None	Unknown	—	+ large spores, endothrix in long chains	T. tonsurans var. crateriforme	Topical	3 yr.; no improvement	3 yr.
XIV	1948	LA	F	17	17	3 mo.	Preg.	One 2-cm. kerion with pus and stubs	None	None	Unknown	—	+ endothrix, square spores in chains	T. tonsurans var. sulfureum	Topical	Cured in 5 mo.	2 yr.
XV	1948	LA	M	17	11	6 yr.	..	Black dots and stubs	Body	None	Unknown	—	+ large spores endothrix	T. tonsurans var. sulfureum	Topical	9 yr. topical treatment; no improvement	3 yr.
XVI	1948	AA	F	18	14	4 yr.	M	Pustules with stubs; area of partial baldness; black dot	Shoulder, arms, legs	None	Unknown	—	+ large spores square, in chains	T. tonsurans var. sulfureum	Topical	7 yr. topical treatment; no improvement	3 yr.
XVII	1949	LA	F	13	13	8 mo.	M	Disseminated black dot with stubs	None	None	Unknown	—	+ inside of hair stub replaced by a mass of spores, endothrix	T. violaceum	Roentgen epilation	Cured	2 yr.
XVIII	1950	LA	F	17	17	7 mo.	M	Granuloma trichophyticum with canalizing sinuses	None	None	Unknown	—	+ large spores, endothrix in chains	T. tonsurans var. sulfureum	Topical	Cured	8 mo.

56 replies and negative in 17; 8 submitted no opinion. The 30 affirmative answers were based on 195 cases and the 17 negative responses on 39 cases (excluding my 39 cases of tinea capitis and the 48 cases of favus). Various comments on the difference were as follows: "fewer areas involved," "less evidence of the disease," "less patchy effects," "minimal loss of hair," "mimicking of other scalp infections," "milder and easier to cure."

The question whether the clinical picture of tinea capitis in the adolescent differed from that seen in children was answered in the affirmative in 17 replies and in the negative in 10 replies, based on 173 and 139 cases, respectively. In my

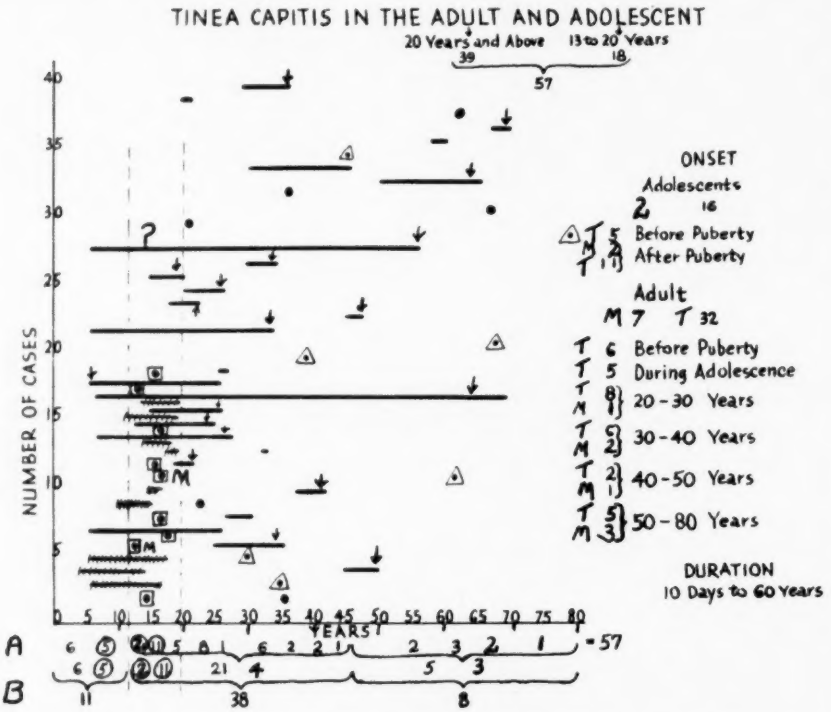

Fig. 2.—Tinea capitis in the adult and the adolescent. Age at first visit is indicated by arrows. Dotted square and divided line indicate Trichophyton infections in adolescents. Dotted square over *M* indicates Microsporum infections in adolescents. Solid line and large dots indicate adult infections with Trichophyton. Dotted triangle indicates adult infections with Microsporum. *T* is Trichophyton, and *M*, Microsporum. ? indicates questionable onset. For explanation of lines *A* and *B*, see text.

experience the clinical picture of tinea capitis in young adolescents (13 or 14 years old) closely simulated that commonly seen in children, while in older adolescents (17 to 19 years of age) it conformed to the adult picture.

REPORT OF CASES

During the past 20 years, from 1931 to 1951, I observed 1,304 cases of tinea capitis in private practice. In every instance the clinical diagnosis was confirmed

by microscopic observations; otherwise the case was not considered one of ringworm of the scalp. Of the 1,304 cases, 64 (4.9%) were encountered in patients after puberty. During the first 10 years of this period I saw 252 tinea capitis cases, of which 12 (4.7%) were in postpuberal persons. During the last decade I observed 1,052 cases of ringworm of the scalp, 52 (5%) in persons over 13 years of age. In 7 of the 64 postpuberal cases the records were incomplete, particularly in regard to cultural data. These cases were eliminated and the pertinent data on the remaining 57 cases are presented in Tables 1 and 2 and Figure 2. Thirty-nine of the patients were adults (over 20 years of age), and 18 were adolescents (ranging in age from 13 to 19 years). Fifty-one were females, 37 of these being adults, and 6 were males. There were 28 Anglo-Americans, 28 Latin-Americans, and 1 Negro.

Figure 2 indicates the age at onset, the duration, and the age at the first visit (indicated by arrows). The number of patients acquiring the infection during each decade of life (line A), before puberty, between the ages of 13 and 45, and after the menopause, is indicated at the bottom of this figure (line B).

MYCOLOGICAL STUDIES

Examination of the Clinical Material.—The clinical diagnosis of tinea capitis was confirmed in 64 postpuberal patients by microscopic demonstration of the causative elements in the form of spores (with or without filaments) around or in the hair. In no instance was the clinical diagnosis confirmed by the finding of the spores or filaments in the scales alone. The scales were rarely examined microscopically or culturally, the clinical diagnosis being substantiated by demonstration of the causative organism in a diseased stub of hair (hereafter referred as stub). When confronted with the frank inflammatory type of lesion, as the kerion or granuloma trichophyticum, examination of carefully selected stubs yielded more satisfactory results than that of the pus or serum, which often proved too time-consuming and unrewarding.

The microscopic examination of infected stubs from the adult scalp revealed changes similar to those encountered in such material from the scalp of children.

The spore arrangement in the hair stubs infected with Trichophyton endothrix followed one of two patterns. In one type the spores were closely packed, oftentimes obliterating the normal structures of the hair shaft, with little or no tendency to chain formation. This was especially observed in the four patients infected with Trichophyton violaceum. This same packing of spores, however, was frequently encountered in stubs of hair infected with the varieties of the T. tonsurans (crateriforme) species group, and was noted especially in infections due to Trichophyton sulfureum and T. tonsurans (crateriforme). This packing, with partial destruction and replacement of the hair shaft, makes the hair very brittle and easily broken off at the skin level, giving the characteristic black-dot clinical type so commonly encountered in the endothrix group.

In other instances the shaft was sparsely involved; the large or rectangular spores were arranged in chains, often giving the effect of a string of beads located just beneath the surface or deeper in the shaft of the hair. With this type of spore involvement the stubs were much longer, at times reaching a length of 1 cm., the average length being 4 to 5 mm. However, frequently short stubs projecting no more than 2 mm. above the skin were encountered. In dealing with the endothrix

organisms, there was found to be a definite relation between the length of the stub and the extent of the spore involvement—the more spores, the shorter the stubs.

In the majority of cases, a number of carefully selected stubs were pulled, picked, or teased out, bottled, labeled, and stored in total darkness. Such a bank of viable stubs at hand greatly facilitated reculturing in cases of initial failure or securing mycologic consultation when classification problems arose or when unusual variants were encountered.

In a high percentage of instances stubs containing the organism of the T. tonsurans (crateriforme) species group will remain viable and yield cultures for up to two years if stored in a bottle in darkness. These findings are particularly interesting if compared with the report of Glass [9] in regard to the viability of hair infected with Microsporum lanosum and Microsporum audouini, the latter being viable after 460 days of storage. In all probability the period of viability can be extended if the material is stored in an air-tight rubber-stoppered tube containing a moist cotton pellet. For the past year I have employed this method, using discarded glass cartridge ampuls formerly containing procaine hydrochloride.

Cultural Studies.—Planting a single diseased stub on a modified Sabouraud's medium gave a high percentage of successful primary cultures with few contaminants. This method proved far superior to scrapping over the lesion and planting scales, debris, and stubs, as it resulted in a higher percentage of contaminant-free pure cultures, which obviated reculturing. If carefully selected stubs from beneath scales or crusts at the periphery of the kerion did not yield organisms, wiping over the surface of the inflammatory lesion with gauze or the back of a knife blade, exerting slight pressure during the stroke, frequently produced suitable material in the form of short stubs.

On the first visit, a minimum of six cultures from different areas of the inflammatory lesion was made. Spreading the pus, blood, or serum over the surface of the medium often yielded positive cultures. In other instances it was necessary to bite out a piece of tissue with a small mouse-toothed forceps, selecting a depression or dimple in the kerion or granuloma trichophyticum as the best site from which to obtain such material for planting.

In dealing with the T. sulfureum variety, certain sugars, as well as some commercially available commonly used peptones, do not allow the development of the sulfur-yellow color. A very satisfactory modified Sabouraud's culture medium, as suggested by Lewis and Hopper,[10] allowing the development of the proper color in the colony, contained the following ingredients:

Agar (granular)	18 gm.
Peptone (difco®)	10 gm.
Dextrose (technical)	40 gm.
Distilled water	1,000 cc.

Such a medium bottled and ready for use is commercially available.[11] The routine use of this medium over the past three years has established its uniformity.

9. Glass, F. A.: Viability of Fungus in Hairs from Patients with Tinea Capitis, Arch. Dermat. & Syph. **57**:122 (Jan.) 1948.

10. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Ed. 3, Chicago, The Year Book Publishers, Inc., 1948, p. 250.

11. Derm Medical Company, P. O. Box 8442, Los Angeles 16

From the 64 patients encountered, 57 pathogenic fungi were isolated on modified Sabouraud's medium, 53 of which were classified as to the species. In many instances reculturing was necessary to determine the species. In four patients, the organisms were classified only as to species groups, because of the difficulty in segregating the varieties of organisms falling in the T. tonsurans group.

Table 3 provides a breakdown of the results of the mycologic studies in the 57 patients.

Cultural Characteristics.—The Microsporum species, Trichophyton mentagrophytes, and T. violaceum isolated culturally from the scalps of adults behave true to type. Some of these forms are so commonly encountered and the cultural characteristics of others are so classical that they will not be discussed here. However, the mycologic characteristics of members of the T. tonsurans (crateriforme) group,

TABLE 3.—*Results of Cultures in Cases of Postpuberal Tinea Capitis*

Organism				
Group	Species	Adults	Adolescents	Total
Microsporums		7	2	9
	Audouini	1	..	1
	Lanosum	6	2	8
Trichophytons		32	16	48
Faviforme	Violaceum	2	2	4
Gypseum	Mentagrophytes	1	1	2
Tonsurans (crateriforme)		29	13	42
	Tonsurans (crateriforme)	9	5	14
	Sulfureum	16	6	22
	Epilans (cerebriforme)		1	1
	Sabouraudi (acuminatum)	1	..	1
Unidentified as to species		3	1	4
Total		39	18	57

because of their infrequent occurrence in certain localities, are of interest and warrant a brief review.

Mycologic Characteristics of the T. Tonsurans (Crateriforme) Species Group: Differentiation within this group was made mainly on the gross cultural characteristics, as the microscopic morphology in cultural mounts was very similar. This species identification was of no practical importance, since there was no relationship of any variant to a particular type of clinical picture. This segregation did not affect the prognosis, course, or treatment. From the practical clinical standpoint it made little difference whether the culture was heaped or sunken in the center, smooth or folded, velvety or powdery, white or creamy, beige, brown, yellow, or tinted with rose or red. However, it is important to realize that these variations exist and are possible in this species group. Gonzalez Ochoa and Romo Vasquez,[6] Kligman and Constant,[2p] and others are all in accord with the species group name of T. tonsurans and include in it (1) T. tonsurans (crateriforme); (2) T. sulfureum; (3) Trichophyton epilans (cerebriforme), and (4) T. sabouraudi (acuminatum). Carrion and Silva,[7] in their discussion on T. tonsurans, included all these varieties in this

group except T. sulfureum. Conant and associates [12] placed the four above varieties in the same broad group but entitled it "the crateriform group."

Many cultures were studied, using the battery of infected stubs for repeated culturing. Each primary isolate was obtained by planting an infected stub on the modified Sabouraud's medium. I found that the gross cultural picture varied considerably but remained fairly constant if infected stubs were used for reculturing rather than subculturing. Subculturing, sectoring, and replanting produced cultural patterns of many transitional types. Some varieties would shift from one species pattern to another, as well as change color and in some instances lose the pigment entirely when repeatedly subcultured.

The cultural characteristics described under the T. tonsurans species group were the commonest encountered in this study. The description is based on studies on 38 patients, the offending Trichophyton occurring as the tonsurans 14 times, the sulfureum 22 times, and the sabouraudi and the epilans once each.

(*a*) Gross cultural characteristics: The rate of growth of the entire T. tonsurans (crateriforme) species group was slower than that of other dermatophytes, and it differed considerably with the variants encountered in this group. In three to five days the T. sulfureum variety and in seven to nine days the T. tonsurans (crateriforme) variant developed hairy-like white projections at the sides of the implanted stub. In the case of the T. tonsurans (crateriforme) variant, a creamy-white, velvety, nummular colony developed which eventually assumed the characteristic central depressed crater.

The surface pattern of the colony varied markedly in this group. In some colonies, a central elevation of 3 to 4 mm. developed (acuminatum variety), with a smooth surface sloping toward the border. In another, ridges radiated from the central knob to the borders and became multiply folded and irregularly arranged (cerebriform variety). The color was often cream to light yellow.

In others, the color of the colony was the predominant diagnostic feature, as in the case of the T. sulfureum variety. The development of this variant often followed a fairly uniform course. On the third or fourth day, sparse white fluffy hairy-like projections could be seen growing from the sides of the implanted hair. By the fifth or sixth day, a yellowish-brown tuft was discernible in the surrounding white fuzzy portion of the colony. Owing to the rapidity of growth and the yellow color, it was very suggestive of M. lanosum, but the growth of the latter was always more luxuriant and rapid, and usually the color was a lighter yellow. At the end of the first week, a light red or pink nodule appeared in some instances in the center of the powdery bright yellow portion of the colony, which usually measured at this time about 1.0 to 1.5 cm. in diameter and was surrounded by a white creamy zone bordered by an amber-colored halo. The above color zones were best demonstrated when observed by transmitted light. The reverse of the colonies showed the characteristic yellowish-brown, always being darker at the center. Ten to 12 days after planting, a grayish-white powdery effect developed around the yellow center. During the next week varying shades of yellow in concentric rings developed, the center being a bright yellow with a pale yellow halo encircled by a broad zone intermixed

12. Conant, N. F., and others: Manual of Clinical Mycology (Military Medical Manual), Philadelphia, W. B. Saunders Company, 1944.

with light yellowish-green and gray. About this time a light pink cast developed over the powdery surface. The aerial growth was scant and dry, and the surface was finely powdered with the ever-present light filamentous amber halo at the periphery. In some variants the colony remained flat during the next two weeks, while in other instances it became folded, with the development of irregular radial grooves or convolutions, the crests of these being studded with yellowish sulfur-like granules. Eventually the entire colony assumed the characteristic yellow sulfur-like color, which was retained. Older colonies often had speckled cream to light brown tufts throughout the central portion. At six weeks of age a muddy brownish-yellow color developed, with the lighter tufts scattered over the central zone.

(*b*) Culture mount: Microscopically this group showed the usual characteristics of the genus Trichophyton, that is, microconidia *en thyrses* and *en grappes*. Chlamydospores were seen in varying numbers, while macroconidia were few but were observed.

(*c*) Cultures examined under the Wood light: Under the filtered ultraviolet rays there was also noted a great variation in the appearance of the colonies of the variants. The appearance depended on the age of the culture. A colony of the T. tonsurans group on modified Sabouraud's medium in a Petri dish or Kolle flask measured 4 mm. on the fifth day, showing up as a light lavender color surrounded by a narrow white zone when examined under the filtered ultraviolet rays. On the 8th or 10th day, a white island appeared in the lavender zone, which was surrounded by a yellowish-green band. A two-week-old colony showed three concentric zones, the central one a light green or a drab olive with a light white ring, surrounded by an outer lavender or orchid zone. At four weeks of age a typical colony measured 5 to 7 cm. in diameter and was composed of multiple concentric zones varying in width. The center was tan or drab olive and was separated from the orchid or lavender zone by a lighter band. Two light yellowish-green zones were separated by a light orchid ring. A bright yellowish-green brilliantly fluorescent narrow ring separated the peripheral filamentous orchid halo from the outer light yellowish-green zone. At six to seven weeks of age, the entire colony was a drab olive-green or a reddish-chocolate color studded with lighter tufts.

Other colonies did not have the above-described brilliant multiply zoned characteristics at the various stages of growth, but appeared drab green throughout with ill-defined light and dark green zones. At six weeks of age the major portion of the colony was a deep reddish-chocolate color with a narrow olive-green peripheral zone.

Specimens of hair and/or cultures from a number of these patients were examined and studied by expert mycologists, such as Emmons, Hopkins and Benham, Kligman, Lewis and Hopper, and Lamb. Kligman, at the University of Pennsylvania, made an exhaustive mycological study, using five different media on approximately one-third of the tonsurans organisms isolated from these adult scalps. This material was furnished from our infected-stub bank. There were no unusual mycological features found in this study, but the usual variations as commonly encountered in this species group were elicited. This was done to corroborate my classification of the various organisms and also to determine if by chance unusual mycologic traits of these fungi could account for the high incidence of postpuberal

tinea capitis. Without exception, every mycologist reported nothing unusual in the cultural characteristics or behavior of these strains isolated from adult scalps.

All the organisms cultured from adult and adolescent scalps compared favorably with like organisms isolated from the scalps of children. In instances in which an adult and a child in the same family were infected, cultures from both persons were identical, no variations being observed in primary cultures.

CLINICAL CONSIDERATION AND COURSE

The clinical manifestations of tinea capitis in the adult, as in children, are to a great extent determined by the species and/or the species group of the causative fungus.

TABLE 4.—*Incidence of Clinical Signs and Symptoms in Thirty-Nine Cases of Tinea Capitis in Adults*

Group / Species		Organisms					Total 39
		7 Microsporums		32 Trichophytons			
		Audouini	Lanosum	Tonsurans Group	Gypseum (Mentagrophytes)	Faviforme (Violaceum)	
No. of Cases		1	6	29	1	2	39
Signs	Frequency, %						
Hair loss, Scaling, Stubs	100	1	6	29	1	2	
Folliculitis	30	..	..	12	..	1	
Black dots	25	..	..	10	..	2	
Furuncles	12	..	..	5	..	..	
Kerion	5	..	..	2	..	..	
Granuloma trichophyticum	5	..	..	2	1	..	
Lupus-erythematosus-like lesions	5	..	..	2	..	..	
Cicatrizing, scarring, with atrophy	5	..	..	2	..	..	
Glabrous skin lesions	59	..	4	19	1	..	
Tinea unguium	25	..	..	8	..	..	
Symptoms	Instances						
Asymptomatic	12	..	..	..	..	..	
Itching	13	..	..	..	..	..	
Soreness	11	..	..	..	..	..	
Very painful	3	..	..	..	..	..	

Table 4 gives the incidence of various signs and symptoms in the adult group.

The clinical pictures encountered can be advantageously discussed under the following headings and subgroups.

The Microsporum Infections.—With a few exceptions, Microsporum scalp lesions in the postpuberal patient and in the child were similar in appearance. After puberty gross patchy lesions were not so evident, were fewer, and were less likely to exhibit subjective or objective inflammation. The hair loss at times followed the pattern of a generalized thinning. Nevertheless, in the majority of the cases, in spite of an absence of inflammatory reaction, the involved hairs were very loose. Consequently, loss of the infected stubs was often rapid and marked, and recovery usually was prompt.

(*A*) M. Audouini: In a single case, that of a Negro woman aged 39 (Case 19), the causative organism was M. audouini. Clinically the infection was typical "gray-

patch" ringworm. The patient presented the characteristic discrete patches of partial alopecia, with gray scaling and stumps of hair covering the area. There was complete absence of an inflammatory element, yet the stubs were quite loose. Examination of the infected stubs under the Wood light showed the characteristic clear green fluorescence. There were no glabrous skin lesions. A cure was effected in three months by manual epilation with tweezers, frequent washing and brushing and the use of an inflammation-enhancing antiparasitic preparation, Formula No. 2 (3% salicylic acid, 5% ammoniated mercury, and 10% precipitated sulfur).

This woman had not menstruated for five years because of a panhysterectomy performed for an extensive leiomyoma of the uterus. The ovaries were left *in situ* and were reported to appear normal.

(*B*) M. Lanosum (Canis; Felineum): Cultures for six adult and two adolescent patients with scalp infections and hair involvement yielded M. lanosum. Two of the adults (Cases 2 and 4) exhibited a single scaly patch with stubs, with no lesions on the glabrous skin. Both patients had acquired the infection from their daughters, who had multiple discrete patches with stubby tight hair throughout the areas. The same organism was isolated from the mothers' and the daughters' scalps. The infection in the children had been present for months. The hair stumps located throughout the patches in the scalps of the adults were very loose, and the patients responded promptly to pulling, brushing, and application of a mild parasiticide, with clearing in four and six weeks, respectively.

One adult (Case 34) presented a round, smooth, truly bald lesion which measured 3.5 cm. in diameter. There were no stubs in the center of this lesion; however, a few very loose stubs measuring 3 to 4 mm. in length were scattered at the margin of the patch. They were barely detectable with the aid of a binocular loop by direct examination but fluoresced a bright yellowish color under the Wood light. This single bald area in a 45-year-old nervous woman, suddenly appearing during the menopause, had been diagnosed and treated as alopecia areata by a competent dermatologist. The patient suspected the correct diagnosis when a pruritic circinate lesion developed on her shoulder.

Three other scalp infections due to M. lanosum (Cases 10, 20, and 28) occurred in elderly women, aged 62, 68, and 79, respectively. Each exhibited marked generalized loss of hair, with stubs scattered irregularly over the entire scalp throughout the intervening normal long hair. There were no bald patches as are commonly seen when this entity is encountered in children. There was no inflammatory reaction evident, yet the infected stubs were very loose over the entire scalp. This accounted for the unusual clinical picture of a marked hair loss and generalized thinning, as illustrated in Figure 3.

All three of these patients contracted the infection by sleeping with kittens. This massive implantation of the animal type of fungus explains the multiple glabrous skin lesions found in all three patients, with eyebrow and eyelash involvement in two of them. Response to brushing, washing, and application of a mild antiparasitic ointment was rapid because of the looseness of the stubs, cure occurring in four, five, and seven weeks respectively.

Two adolescent patients (Cases V and XI) with infection due to M. lanosum presented typical multiple scaly patches with stumps throughout the areas. Both

infections responded in about the usual fashion and time to brushing, washing, and local medication.

The Trichophyton Infections.—(*A*) Ectothrix Type: 1. T. mentagrophytes (gypseum): In two instances in this series, the scalp and hair were infected with T. mentagrophytes.

A 62-year-old white man, a rancher by occupation, presented a palm-sized 6- by 8-cm. lesion to the left of the vertex (Case 37). The major portion of the lesion was crusted, and irregular thinning of the hair was evident. Above the center of this large patch was located an elevated spongy 2.5- by 5-cm. sessile swelling which was almost bald except for a few long, normal-appearing, widely separated hairs. Serum oozed from around a few short stubs near the scaly crusted borders

Fig. 3 (Case 28).—Patient aged 79, showing generalized thinning of hair with noninflammatory M. lanosum type tinea capitis. Infected stubs are loose.

of the sessile portion of the lesion. A giant circinate lesion involved the left cheek and neck and extended posteriorly into the hairline of the scalp. The causative organisms were easily demonstrated in skin scrapings from the cheek, neck, and scalp in the form of filaments; however, carefully selected specimens from the rim of the inflammatory scalp lesion had to be examined repeatedly before a stub with the characteristic collar of spores was found. The infected stubs did not fluoresce under the Wood light. No infected hair was found, nor was fluorescence observed in the beard.

The rancher's saddle horse had a scaly, partially bald 4- by 6-cm. patch on the right shoulder, and the infection was probably contracted from this source. Cultures from the infected hair from the patient and the horse revealed a fluffy type of T. mentagrophytes.

The giant ringed lesion on the face, of six weeks' duration, regressed under treatment with weak tincture of iodine; the scalp granuloma, of three months' duration, responded in two months to use of hot packs and ammoniated mercury ointment and administration of saturated solution of potassium iodide by mouth. The patient has remained well for six months.

The other ectothrix infection caused by T. mentagrophytes occurred in a 17-year-old boy (Case X), who had a typical single raised kerion Celsi 3 cm. in diameter. The lesion disappeared in seven weeks, during which time he received strong iodine solution by mouth and used hot packs and ammoniated mercury ointment locally.

(*B*) Endothrix Type: 1. Faviforme group: T. violaceum was isolated from the scalp of two adults and two adolescents. All patients (Cases 6, 26, III, and XVII) presented the typical black-dot type of ringworm of the scalp as observed in children. Both adults refused roentgen epilation and when last observed were still infected, as local treatment proved of no avail. The adolescent patients were epilated and cured. One has been observed over a 13-year period after treatment and the other for two years.

2. T. tonsurans (crateriforme) species group: This group was the most commonly isolated in the series, being identified 29 times (75%) in the adult group of 39 patients and 13 times (72%) in the adolescent group of 18 patients.

From the clinical standpoint, this entire group is an enigma, particularly when encountered in the adult scalp. This species group may be considered a hybrid, having the inflammation-producing potentialities of the zoophilic organisms, yet also possessing characteristics of the faviforme group, such as its ability to destroy tissue, with resultant scarring and atrophy, and its tendency to persist over the years and to attack the adult. Because of these inherent characteristics, any one of this species group may produce a variety of bizarre clinical manifestations, frequently not resembling the usual picture of ringworm of the scalp in the least, but often mimicking other diseases, such as an ordinary coccigenic folliculitis, folliculitis decalvans, chronic recurrent small furuncles, a canalizing pyogenic infection, or even lupus erythematosus.

Rarely, the picture of the tonsurans infection in the adult may simulate the classic picture of tinea capitis usually seen in the child, fitting into one of the two distinctive forms, namely, (1) the "disseminated" ringworm (Alder-Smith) or (2) the black-dot type of ringworm.

The most striking feature of the clinical picture observed in the present series was the great variability, the classic forms being the exception rather than the rule. On the one hand, the scalp may appear to be perfectly normal except for a very few (at times no more than four to six) short stubs, measuring 2 or 3 mm. in length, inconspicuously scattered among long normal hair. Oftentimes, there is no inflammatory element and the chronic infection is asymptomatic; this occurred in 12 cases in the series.

Some mothers acquired the infection from their children, yet the symptoms were so mild that they did not recognize it. Some few may harbor the infection and later experience a spontaneous cure. In another adult, the same species of this tonsurans group may produce an acute destructive inflammatory granuloma. The many clinical gradations encountered between the two extremes in this series of 42 patients infected with the T. tonsurans group of organism are detailed below.

(*a*) Invasion of the scalp and hair follicle. The erythematous scaly patch with involvement of the epidermis of the scalp and the hair follicle before the hair proper is invaded, which has been described as the initial lesion, was not observed. Microscopic examination and cultural studies were made on several occasions on exposed mothers whose children had multiple lesions due to infection with the tonsurans group. In no instance was the fungus recovered from the mother's scalp until stubs developed. In two mothers, while under surveillance, infected stubs developed after exposure to their children. Identical organisms were isolated from the scalps of the mothers and the children.

(*b*) Invasion of the hair. This probably occurs early and very rapidly. In the two mothers mentioned above 10 days and two weeks were the intervals between negative and positive results on examinations. In both instances the causative organism was demonstrated in cultures from stubs.

(*c*) The inflammatory phase (objective phase). Over the scalp the unaffected hair of normal length was irregularly interspersed with varying numbers of the ever-present telltale infected stubs associated with varying degrees of inflammation, manifested in the following ways:

(1) As a mild inflammatory, seborrheic-like generalized scaling associated with thinning, which is often linear. In some cases the scaling was very dry and furfuraceous. The short, lusterless stubs were often few and inconspicuously located under these scales. Black dots, varying in number and scattered over the scalp, in some instances simulated the clinical type commonly caused by T. violaceum and were distinguishable only by cultural means.

(2) As an obvious inflammatory reaction, in the form of a perifollicular erythematous areola with the short stub (1 to 3 mm. in length) protruding from the center. If the inflammatory reaction is more marked, the accompanying edema may engulf the short stub, making it less discernible.

(3) As multiple areas of folliculitis or small furuncles, with or without short stubs protruding, this depending upon the original length of the stub and the degree of the inflammation and accompanying edema.

(4) As a kerion celsi. This was unusual in the adult, occurring twice (5%), but was more frequent in the adolescent, occurring in three instances (18%).

(5) As a granuloma trichophyticum. Two phases were noted, namely, the early and the late stages. One patient (Case 38; Fig. 4), after a chronic course of seven weeks of a superficial T. tonsurans (var. sulfureum) infection, exhibited a conglomerate mass of papules and nodules over each parietal region. These red to reddish-purple nodules were 0.5 to 1 cm. in diameter, spongy, and only slightly painful to pressure. Later in the course, these large nodules coalesced, forming boggy sessile or dome-shaped swellings. A portion of this granuloma became traversed by burrowing or canalizing fluctuant tracts which contained mucopurulent grumous sterile fluid. The surface of the nodular masses and dome-shaped swellings was devoid of hair, with the exception of a few stubs 0.5 to 1 cm. in length, irregularly scattered throughout the lesion. There was no evidence of a folliculitis, and pus could not be squeezed from around the stubs, as is customary in a true kerion. Another patient (Case XVIII) was seen late in the course of the process and presented canalizing tracts 1, 3 to 5 cm. in length, burrowing under

the scalp and opening here and there to form draining sinuses. This picture mimicked perifolliculitis capitis abscedens et suffodiens and had been so diagnosed previously. Large spores (endothrix) were found in stubs of hair at the border of an involved area. T. tonsurans (var. sulfureum) was isolated. I observed such a picture or certain phases of the above-described course in two adults and in two adolescents.

(6) As impetiginized plaques with minimal hair loss studded with stumps under crusts and scales. These were observed in two instances. Severe itching and burning were common complaints in both patients.

(7) As a chronic lupus-erythematosus-like lesion. This assumed either the early or the late form. In one instance (Case 8) an acute erythematous, edematous, sharply demarcated 2- by 3-cm. plaque covered with fine scales was suggestive of

Fig. 4 (Case 38).—Granuloma trichophyticum due to T. tonsurans var. sulfureum.

early lupus erythematosus of the scalp. The ever-present spore containing stubs of hair clarified the diagnosis. This plaque eventually developed into a true kerion, and a cure resulted.

In another instance (Case 21) the fungous infection simulated late lupus erythematosus, being accompanied with atrophy and scarring. There was an attempt to vascularize the sclerotic area with fine telangiectatic vessels extending from the periphery into the partially bald patch. Black dots at the border of the area mimicked follicular plugging and made the lupus erythematosus-like picture complete (Fig. 5). A microscopic study of the ever-present diagnostic stub or hair fragment in the form of "black dots" corroborated the diagnosis of tinea capitis. Cultural studies established the T. tonsurans (var. sulfureum) as the causative fungus. Such lupus-erythematosus-like lesions were tabulated 11 times in the replies [8] to the questionnaire, being mentioned by Dr. C. M. Griswold and Dr. S. S.

Bowen, Dr. J. B. Howell, Dr. C. S. Livingood, Dr. M. Polsky, and Dr. J. B. Shelmire, all of Texas, and Dr. J. Walter Wilson, of California. Dr. Kenneth Baker, Dr. A. C. Curtis, and Dr. T. H. Diseker noted similar lupus-erythematosus-like pictures in favus.

(*d*) The healing phase. Scarring and atrophy were at times negligible and in other instances very pronounced, with permanent hair loss. These were variable characteristics, depending upon the type of fungus, the amount of secondary pyogenic infection, and the patient's reaction to these offending organisms.

Hair loss was also variable. In some patients, only one or two hairs were involved here and there, manifested as stubs or dots which were not detectable except upon the most careful inspection in daylight and with the helpful aid of a

Fig. 5 (Case 21).—T. tonsurans (var. sulfureum) infection of scalp. Chronic lupus-erythematosus-like picture with (1) atrophy and scarring; (2) black dots mimicking follicular plugging.

binocular loop. The black-dot manifestation was commoner over points of pressure where the involved hairs were rubbed off, with very small, partly bald patches resulting. On the other hand, the hair loss was occasionally extreme and the partially bald patches approached palm size. Angulated, square, and, at times, linear finger-like partly bald patches were the rule, and these tended to be small.

TRICHOPHYTIN TESTS

The Trichophytin test was done on 8 of the patients with noninflammatory lesions and on 12 of the persons with inflammatory lesions. The reaction to the test was negative on all with noninflammatory lesions, with one exception. In this patient (Case XII) the reaction was very strongly positive. The test reaction was positive for all patients with the inflammatory element.

GLABROUS SKIN LESIONS AND NAIL INVOLVEMENT

Concomitant glabrous skin lesions and nail involvement were commonly encountered in both the adult and the adolescent patients with tinea capitis. Locations of the glabrous skin lesions, in order of frequency, were the nape of the neck, the sides of the neck, the face, the shoulders, the arms, the body, and the hands (occurring on the dorsa of the hands and wrists in two instances [Cases 11 and 14]).

Four of the six adults (66%) and one of the two adolescents with tinea capitis due to M. lanosum had glabrous skin lesions.

Of the 32 adults with Trichophyton scalp infections, 19 (59%) had glabrous skin lesions. Six of these also had onychomycosis. Two other patients had only fingernail involvement, making a total of eight adults (25%) with tinea unguium complicating tinea capitis.

Of the 16 adolescents with Trichophyton infections, 8 (50%) had glabrous skin lesions and 2 of these had fingernail involvement, making a total of 3 patients (18%) with onychomycosis complicating tinea capitis in the adolescent.

The disease of the smooth skin caused by the zoophilic M. lanosum always appeared as circinate lesions. Such ringed lesions often accompanied Trichophyton lesions of the skin, but in two of these patients giant gyrate ring lesions were observed. In two instances chronic scaly plaques which simulated neurodermatitis involved the nape of the neck. Two patients presented plaques resembling chronic psoriasis. A 22-year-old woman (Case 11) had three nummular eczema-like patches on the dorsum of the hand and the wrist. The fungus was probably inoculated into the skin from the scalp through her habit of resting the head on the hands. Filaments were demonstrated in scrapings from all these lesions.

SOURCE OF INFECTION

Three of the six M. lanosum scalp infections in adults and two M. lanosum scalp infections in the adolescents were contracted from kittens. Three adults definitely acquired their infection from children. The one M. audouini scalp infection was probably contracted from a child.

Of the Trichophyton scalp infections in the adults, the source of the infection was unknown in 12 instances. Acquiring the infection from contact with other members of the household was the commonest known source, seven infections being contracted from children, one from a grandchild, one from a niece, and one from the mother. In four known instances adults infected children.

Acquiring the infection first on the nails from beauty parlors, with subsequent infection of the scalp, was observed in three instances in the adults. This was not observed in the adolescents. Beauty operations were blamed as a possible direct source of the scalp infection in six instances. Five women felt that they had acquired the infection from beauty parlors and one that she had acquired the infection from a maid with onychomycosis who had repeatedly dressed her hair. In this instance (Case 9) the same organism, T. tonsurans (var. sulfureum), was isolated from the scalp of the employer and the nail of the maid. A beauty parlor operator (Case 7) acquired the infection in her nails from manicuring the infected nails of a customer. She infected her own scalp and presumably the scalp of an 11-year-old child. The organisms from her nails, her scalp, and the child's scalp were the same, T. tonsurans (var. sulfureum).

In 13 instances of the Trichophyton scalp infections in the adolescents, the source was unknown. One patient contracted the infection from the cap of a band uniform, one from cattle, and one from a sister.

T. mentagrophytes infections were acquired by one adult from a horse and by one adolescent boy from a calf.

HORMONAL AND ENDOCRINE INFLUENCE

For many years there has been a feeling that hormonal or endocrine influence brought about some change in the scalp at puberty that made the skin unsuitable for the growth of fungi. Sabouraud [13] pointed out that Trichophyton infections usually heal at puberty because the skin surface is at that time "unfit" for fungous growth and reproduction. Maschkilleisson [3] suggested a connection between chronic tinea capitis in the adult and a dysfunction of the endocrine system. Rothman, Smiljanic, and Weitkamp [14] explained the immunity of the adult to fungous infections of the scalp on the basis that the hair fat of the adult is five times as fungistatic as that of children. This fungistatic action probably does play a part in preventing infection of the adult scalp with M. audouini. During the severe nationwide epidemic of the past few years due to this organism, there were relatively very few infections of adults. A specific example of this was brought out by Dr. E. D. Osborne,[8] Buffalo, who stated in his reply to the questionnaire that he had observed 6,000 scalps of children infected with M. audouini during this epidemic but had not seen one infected adult scalp. Apparently, however, this fungistatic action does not apply to such a great extent to other organisms, such as M. lanosum, T, mentagrophytes, the faviforme group, and particularly the T. tonsurans (crateriforme) group.

In this series of patients, I did not observe a spontaneous cure; however, this possibly may occur. I have noticed that the clinical picture in the young adolescent is similar to that in the child, while as the person approaches adulthood the manifestation of the fungous infection becomes more like that encountered in the adult. I have also observed in a few instances that the clinical picture was altered at puberty, becoming insignificant and settling down to a dormant state, bringing about the unique and precarious situation in which a seemingly healthy person harbors a pathogenic organism in its normal site without producing the gross symptoms of the disease usually associated with that organism.

Several other facts brought out in this series of patients tend to discount hormonal and endocrine effects as being the only explanation for the partial immunity of the postpuberal scalp to some fungi. In the first place, 38 of the 57 (66%) patients acquired the scalp infection during the period of life that the gonads and glands of internal secretion are most active, namely, between the ages of 13 and 45, inclusive. Only 19 (i. e., 11 prepuberal and 8 postmenopausal) patients, or 33%, were infected during the period that one would expect the endocrine glands to have the minimum effect on the skin. In considering this fact, one would have to take into consideration the greater possibility of exposure of a mother during the child-rearing age, as well as the number of persons in each age range.

13. Sabouraud, R.: Les teignes, Paris, Masson & Cie, 1910.

14. Rothman, S.; Smiljanic, A. M., and Weitkamp, A. W.: Mechanism of Spontaneous Cure in Puberty of Ringworm of the Scalp, Science **104**:201 (Aug. 30) 1946.

Of the 41 females in the age range of 13 to 45, inclusive, 34 menstruated regularly, 1 was pregnant (with a previous normal menstrual history), 4 did not menstruate because of hysterectomy, and in 2 the menstrual history was not known. Of the 34 normally menstruating women, 15 had one to nine children, 1 had no children, and 17 were single. The marital status and the child-bearing history were unknown in one instance. Such a high percentage of women with apparently normal menstrual and reproductive functions would indicate that the ovaries were normal and were influencing the skin in the usual and normal fashion. Such a record would seem to be a more accurate indicator of normally functioning ovaries than results of examination of the reproductive organs. In only one patient were there any symptoms indicating hypofunction or dysfunction of the endocrine glands. There were no obese patients, no unusually dry skins, or any other signs or symptoms which would indicate a thyroid deficiency.

Three women (Cases 4, 22, and 26) were treated for several months with female sex hormones; this treatment had no apparent effect on the fungous infection in the scalp.

DIAGNOSIS

The clinical picture presented by the Microsporum infections in the scalp of the postpuberal patients should offer no diagnostic problems. This is especially true when one uses that helpful and essential adjunct, the Wood light. When examined under filtered ultraviolet rays, Microsporum-infected hair in the scalp of all adult and adolescent patients in this series fluoresced in the manner typical of children's scalps infected with these organisms.

Diagnostic difficulties encountered in chronic atypical tinea capitis in the adult and the adolescent, particularly that due to the T. tonsurans species group are forcefully exemplified by the fact that in 8 of the 39 adults and in 2 of the 18 adolescents (17 and 18 years of age) the infections were incorrectly diagnosed by 10 competent dermatologists. The incorrect diagnoses made were folliculitis, three times; seborrheic dermatitis, twice; alopecia areata, twice; lupus erythematosus, perifolliculitis capitis abscedens et suffodiens, and pseudopelade of Broq, once each. In one instance the infection was falsely diagnosed as folliculitis by three different dermatologists for the same patient.

The hazard of improper diagnosis is enhanced if the clinician is laboring under the delusion that tinea capitis is relatively a nonentity after puberty. The index of suspicion of dermatologists must be raised regarding the possibility of ringworm infection of the scalp in the postpuberal patient. The first prerequisite in making the diagnosis is the presence of the entity in one's diagnostic horizon. The majority of the infections were encountered in women with long hair, a factor which made finding the infected stubs more tedious.

This problem is rendered even more difficult by the fact that the Wood light is not a dependable aid in diagnosing Trichophyton infections of the scalp. Hair infected with the ectothrix T. mentagrophytes did not fluoresce when examined under filtered ultraviolet rays. Difficulty was also experienced in demonstrating the usual fluorescence of dots or fragments of hair infected with T. violaceum. This was probably due to the shortness of the stubs, which showed up as whitish-gray dots. When an occasional longer stub was found, a white, lusterless fluorescence was observed.

Examination of an infected scalp under filtered ultraviolet radiation (Wood light) is of little value when one of the T. tonsurans (crateriforme) group is the causative organism. Three Trichophyton infections in postpuberal patients were seen before the Wood light was available. Of the remaining 39 patients (27 adults and 12 adolescents) who were infected with organisms of the tonsurans group and examined under the Wood light, no fluorescence was observed if the hair was black or deeply pigmented. The same lack of fluorescence has been noted for years in children with black hair if the infection was due to a member of the T. tonsurans group. The examination of suitable extracted hairs under the Wood light gave negative results; later the stubs were proved positive for the fungus by microscopic examination, establishing the fact that the infected stubs did not fluoresce.

Three adolescents and six adults had blonde, white, or gray hair, and the infected stub appeared dead-white or gray-white. There was no definite fluorescence, but an odd dead or lusterless appearance was evident, the involved hair having an entirely different appearance from that not involved. In one instance of tinea capitis due to the sulfureum variety of T. tonsurans in a woman with white hair (Case 35), the infected stubs appeared a clear violet under the Wood light. Such a difference was not seen in black-haired patients. In all probability the pigment prevents the perception of the difference. This distinct difference in appearance under filtered ultraviolet radiation makes the Wood light an aid in locating the infected stubs only in a blonde, gray, or white-haired patient when dealing with the T. tonsurans species group. In one instance a gray-haired mother's infected stubs exhibited this gray-white lusterless effect, while hairs from her black-haired child showed no difference between the infected and the noninfected hair. Identical organisms (T. tonsurans var. sulfureum) were isolated from both.

The only infallible, ever-present clue to the diagnosis of tinea capitis in the adult and the adolescent found in every instance in this series was the infected stub of hair. At times this clue was a dot, a speck, or a completely embedded fragment, demonstrable only after it had been dug or teased out with a dull knife. In other instances it was necessary to lift up a scale and dig out a stub or a curled hair from underneath. Loose, easily extracted stubs were selected, as these rewarded the highest percentage of positive results. If the search is diligent and protracted, a stub containing spores will be demonstrated if the patient has tinea capitis, except on two conditions. Rarely, in marked inflammatory lesions, such as a kerion or a granuloma trichophyticum, it is impossible to demonstrate the fungus in a stub. I have had this occur in children, but in this series of cases infected stubs were demonstrated in every instance, regardless of the inflammatory reaction. The other exception, mainly academic, occurs very early in the course of invasion, when the skin of the scalp may be involved before the hair proper has become infected.

Since many of the T. tonsurans infections in the postpuberal patient are asymptomatic, every exposed person in a household should be examined at frequent intervals. Glabrous skin lesions, occurring especially on the face, neck, and arms, as well as tinea unguium, should alert the clinician and encourage routine examinations of the scalp.

TREATMENT AND RESULTS

The same basic principles in the treatment of tinea capitis as are commonly employed for children are applicable to the adult and the adolescent. The rapidity of response depends on the removal of the infected hair, which is influenced by its

looseness, this being augmented by accompanying inflammation and other unknown factors due to the reactivity of the patient. As a rule, the looser the hair, the quicker the response.

Inflammatory ringworm, regardless of the causative organism, is a self-limiting disease. If the inflammation is low grade, any form of therapy which enhances the inflammatory reaction shortens the course. An irritating ointment, as anthralin (Formula No. 1), or a mixture containing 3% salicylic acid, 5% ammoniated mercury, and 10% sulfur (Formula No. 2), seems to be efficacious in this regard. This mixture, suggested by Dr. C. M. Griswold,[8] is theoretically incompatible, but it has proved of virtue in many instances, with no untoward effects, such as increased scarring or uncontrolled infection. Its efficacy is increased if potassium

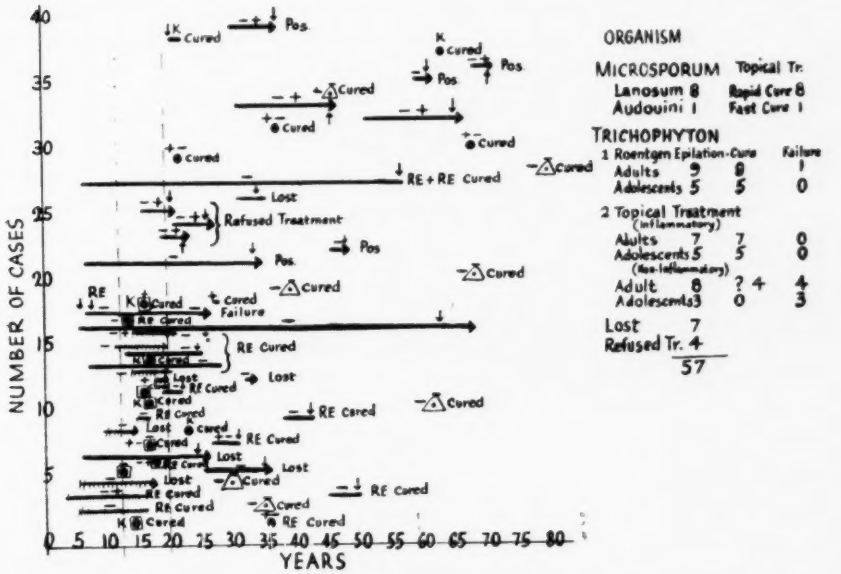

Fig. 6.—Treatment and results in series with tinea capitis. Symbols are explained in legend to Figure 2. Plus sign indicates inflammatory type; minus sign, noninflammatory type; *K*, kerion, and *RE*, roentgen epilation.

iodide or strong iodine solution is given parenterally. Frequent peeling with 95% phenol, neutralized with alcohol, has proved helpful in the treatment of tinea capitis of the localized type in persons of all ages. Peeling by cryotherapy, using solid carbon dioxide or liquid oxygen, has been of aid in the removal of superficial dots and fragments of hair in small localized areas. New fungicidal agents, including those containing undecylenic acid, copper undecylenate, salicylanilide, 5-nitrofurfuryl methyl ether, tetrachloro-para-benzoquinone "spergon," and others, were used in the noninflammatory types of the postpuberal scalp infections due to the endothrix organisms with no cures resulting.

With this in mind, it makes little difference which antiparasitic preparation one uses; however, the method of application is very important. Brushing in the medicament, removing loose hair, always stroking in the direction of the hair growth

to prevent the bending back and breaking off of the stubs, is most advisable. An old soft toothbrush was found best suited. In the kerions, granuloma trichophyticum, and canalizing lesions, recovery was more prompt if frequent hot fomentations and a mild antiseptic ointment were diligently used.

I. *Microsporum Infections.*—Six instances of M. lanosum infection responded in about the usual manner, possibly a little more quickly. One interesting feature was the looseness of the hair in several adults without the presence of any perceptible inflammatory element, which probably accounts for the rapid response. Two adolescent patients (Cases V and XI) responded in about the usual fashion, being cured in six weeks and two months, respectively.

In one instance of M. audouini infection (Case 19) response was very satisfactory in three months' time with the use of Formula No. 2. Vigorous brushing and washing were advised, and this preparation was brushed in three times a day, producing considerable inflammation. The response in this instance was much quicker than that observed in children.

II. *Trichophyton Infections.*—Roentgen epilation offers the most satisfactory method of treatment in the noninflammatory type of the Trichophyton infections of the scalp. Of the nine adults epilated, eight were cured. In all instances the Kienbach-Adamson five-point technique was used, with administration to the adults of 390 to 410 r to each point. The one exception to this dose and the only patient with failure after epilation (Case 26) was a white woman, aged 55, who was partially epilated with roentgen rays, receiving 370 r to five areas. She probably received an underdose, as all the infected stubs or hair could not be removed. Nine months later this patient was reepilated by another dermatologist, receiving 337 r to five areas, this being the second underdose. Defluvium was not complete, but, by diligent and protracted manual removal of stubs over months, a cure was effected. The majority of the adults with average-sized heads received 396 r. One adult, with a large head, a brunette skin, and black hair, received 410 r to the five areas. An average dose of 380 r was delivered to each of the five points in the adolescent patients. A slightly smaller dose was used in five adolescents because all were 16 years of age or younger with one exception (an 18-year-old girl, who had very fair skin and blonde hair).

In these cases, treatment after epilation, with application of the usual adhesive cap, was carried out, using alternately ammoniated mercury and half-strength Whitfield's ointment (an ointment composed of 1 gm. of salicylic acid, 2 gm. of benzoic acid, and 30 gm. of petrolatum). A very important and essential procedure was the mechanical removal of all stubs. This was particularly necessary when black dots, abortive hairs and curls under scales, and fragments and segments of hair broken off flush with the skin were encountered. If these were covered with scales, use of Whitfield's ointment for a few days was advised to expose the remaining stumps. The remaining hairs were removed by strips of adhesive, elastic adhesive tape (elastoplast®), or wax, but many of the stubs had to be individually picked or dug out by means of a dull knife or brushed out with a soft brush if they protruded about the skin.

Seven adults (Cases 8, 18, 29, 30, 31, 37, and 38) and five adolescents (Cases I, XIV, VII, X, and XVIII) recovered while receiving topical treatment, which included brushing, scrubbing, and removal of stubs and the application of inflammation-enhancing antiparasitic preparations. In each instance there was initially a

definite inflammatory reaction, the first five adults having areas of folliculitis and pustules. The last two had granuloma trichophyticum. In these two adults with granuloma trichophyticum lesions, hot boric acid fomentations and a mild mercurial ointment were used, and potassium iodide was given by mouth. Four of the adolescent patients had marked inflammatory lesions, three with large kerions (Cases I, X, and XIV) and one (Case XVIII) with a granuloma trichophyticum. The other adolescent (Case VII), a 17-year-old girl, had a marked folliculitis. In the first five adult patients, brushing with a soft toothbrush was instituted, using Formula No. 1 or No. 2, as indicated in Table 1 or 2, to produce an added amount of inflammation. Iodides were given by mouth in three instances.

Eight adult patients (Cases 17, 21, 22, 32, 33, 35, 36, and 39) did not respond to this local treatment. In Cases 17, 21, and 22, the black-dot feature was predominant. Stubs, black dots, and freedom from inflammation were also observed in Cases 32, 33, 35, 36, and 39.

Four patients (Cases 17, 21, 22, and 32) have been treated long enough to be considered treatment failures. Five patients (Cases 32, 33, 35, 36, and 39) are still receiving various forms of local treatment without satisfactory response to date.

Three adolescent patients (Cases XIII, XV, and XVI) failed to respond to remedies used topically. Two had infections of the noninflammatory type; all had black dots.

Four adult and three adolescent patients were lost, and the outcome is unknown. Of the adults (Cases 5, 6, 12, and 26), three showed the black-dot variety and had had the infection 4, 10, and 20 years, respectively. They had previously received a great deal of topical therapy with no improvement, were disheartened, and would not continue treatment. The fourth adult (Case 26) refused roentgen epilation and was lost after no improvement occurred with eight months' topical treatment. Of the adolescents (Cases IV, VIII, and XII), two had black dots and one was seen only once.

Four patients refused treatment. Three sisters (Cases 23, 24, and 25), aged 22, 26, and 20 years, with extensive disseminated black-dot type infection due to T. tonsurans var. sulfureum, refused to clip their hair and submit to roentgen epilation.

A 68-year-old white woman (Case 16) has harbored the T. sulfureum in her scalp for 60 years, having contracted the infection at the age of 7 or 8 years upon entering school. The scalp infection was of some trouble to her for four or five years but improved at puberty and remained asymptomatic for 55 years. From time to time over these years she has had an occasional circinate lesion on the neck or shoulders. She has refused treatment, stating that the scalp condition is less bother to her than the treatment, which she observed in the case of her daughter (Case 15), whom she had infected at 10 or 12 years of age. The daughter, in turn, later infected her son at 7 years of age. The daughter and her son were epilated by roentgen ray, and both were cured.

The last scalp examination of this patient (Case 16) was made three months ago; during a 20-minute search not more than four short stubs were found. This has been true on many occasions during the past six years. Repeatedly positive results on microscopic examinations reveal the large-spored endothrix sparsely arranged in chains deep in the hair shaft. T. tonsurans var. sulfureum has been isolated on numerous occasions. The same organism was isolated from the scalps of her daughter and grandson.

SUMMARY

A series of 57 cases of tinea capitis encountered after puberty, 39 of these being in adults, is reported and analyzed in respect to incidence, age, sex, age at onset, duration, course, and the hormonal influence on course.

A geographic survey corroborates my experience that tinea capitis in the postpuberal patient, particularly in certain sections of the United States, is not rare. In this area of Texas, 5% of all microscopically diagnosed tinea capitis cases over the past 20 years occurred in postpuberal persons. This high incidence is probably due to the long existence of endemic foci of the endothrix Trichophyton group in Texas and Mexico. This endothrix group of organisms capable of infecting the adult scalp accounted for 46 (82%) of the postpuberal infections in this series. The Trichophyton tonsurans species group was responsible for 42 (91%) of the endothrix infections, 87% of all the Trichophyton infections, and 73% of all cases. The mycologic characteristics of this species group are discussed, and its geographic distribution is cited. The T. tonsurans group produced a variety of bizarre clinical pictures which frequently did not resemble the usual picture of ringworm of the scalp in the least, but mimicked other chronic diseases of the scalp. Concomitant glabrous skin lesions and nail involvement were frequently encountered.

A prerequisite to making the diagnosis is the presence of this entity in one's diagnostic horizon. The only infallible ever-present clue is the infected stub or hair. These stubs are at times engulfed and obscured by the accompanying inflammation, which makes a thorough and diligent search an essential part of the diagnostic procedure. The Wood light is not a dependable diagnostic aid in the T. tonsurans species group of infections. In my experience with this group of organisms, infected black stubs did not fluoresce, and only in the gray, white, or blond-haired patient were infected hairs of a different appearance under filtered ultraviolet rays.

The Microsporum infections presented no treatment problems and responded in the usual fashion to local treatment. Topical treatment in the majority of the T. tonsurans infections was futile, unless a reasonable amount of inflammatory reaction existed at the time the patient first came under observation. Inflammation-enhancing preparations seemed to be a helpful adjunct when fungous infection exhibited only a mild inflammatory reaction.

Adequate epilating doses (390 to 410 r to five points), followed by protracted, diligent manual removal of the stubs, dots, and fragments of hair, is the treatment of choice in the noninflammatory Trichophyton infections.

Dr. C. Ferd Lehmann permitted use of much of his material in this presentation.

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ABSTRACT OF DISCUSSION

Dr. John H. Lamb, Oklahoma City: This is an excellent clinical study on ringworm of the scalp in early and late adult life, carefully checked by laboratory studies. Cultures and microscopic examination of the infected hairs were routine procedures and were carried on in a busy office, the authors studying the cases clinically and then watching the cultures grow.

The varied and bizarre clinical manifestations in the cases reported make all of us suspicious of the many cases of folliculitis and peculiar atrophic lesions of the scalp in adults which we have passed up in our own practice without studying the hairs microscopically or making cultures for fungi.

My colleagues and I have a series of 204 scalp infections seen from 1947 to 1951 in which only three, or 1.5%, of the cultures positive for pathogenic fungi were of the crateriforme group of Trichophyton. This organism is an endothrix, and I agree with the author that this accounts

for its tenacity in living within the hairs in adult life. The sebum with its large quantities of low-boiling-point, saturated fatty acids, as reported by Rothman, cannot exert the selective fungistatic action that it does on the ectothrix groups, particularly M. audouini.

Peck has suggested that sweat also has an influence in the rarity of tinea capitis in adults. In his opinion sweat has a definite influence on the pH of the skin which, in turn, affects the fungistatic action of the fatty acids. Sweat may also contain various quantities of steroids. For example, it is known that sweat contains 50 to 80 γ per 100 cc. of adrenal corticoids.

The conclusion of Dr. Pipkin that hormones do not influence the growth of the endothrix group of organisms in vivo is accepted but does not close the chapter on the hormonal effects on the anthropophilic group of ectothrix fungi in which sweat and fatty acids could have antibiotic effects.

Kingery in 1938 suggested that the hormones should be investigated in this matter of postpuberal immunity to tinea capitis. Roth, Reiss, Dobry, and others have reported fungistatic effects both in vivo and in vitro of estrogens and androgens.

The biologic occurrences of steroids range into the lower forms of animal and plant organisms. Endocrinologists know well the profuse production of estrogens in plants with sexual dimorphism, for example, in the female catkin of the pussy willow. Gonadotropins have also been isolated during the growth stage of oats and Russian onions.

Fontaine and Irving have demonstrated the fungistatic action of tomatin, an extract of the leaves of a South American tomato plant, only recently to find tomatodine, one of the components of the extract, to be of steroid structure and capable of being converted into delta-16-allopregnenolone.

We have repeated this work of Irving and Fontaine and found the impure extract to be antifungicidal as reported. We are in process now of studying other newer steroids, one of which in particular I wish to mention; pregnenolone acetate in preliminary work shows some evidence of being fungistatic in vitro and can be given orally in 150- to 200-mg. doses daily to children without risking precocity or other serious effects.

I believe the chapter is only opening on steroid hormones and their uses in chronic mycoses. Sweat as the agent for carrying the steroids must be further studied by microchemical methods for 17-ketosteroids, and the study of the use of the safer steroids in epidemics of ringworm in children must be completed.

Dr. Bedford Shelmire, Dallas, Texas: One of the female patients in the series reported on by Dr. Pipkin was my older sister. She was treated in my office for 15 years for dandruff. During that entire period her sole complaint was itching of the scalp. Clinically she presented only slight scaling. There was no thinning of the scalp hair and no broken hairs, although no diligent search was made for the latter since tinea capitis was not suspected at that time. At the termination of this 15-year period a single annular lesion at the hairline on the neck gave the first clue to the correct diagnosis. Mycelia were demonstrated in scrapings from the lesion, and T. sulfureum was cultured from scales. A careful examination of the scalp with a magnifying lens revealed scattered broken hairs. These had been overlooked on previous cursory examination. Cultures of the broken hairs produced T. sulfureum.

After five years of treatment with various local applications, this patient was sent to Dr. Lehmann and Dr. Pipkin for x-ray epilation. At the end of approximately three weeks there was a complete defluvium of the unaffected hairs, but the scalp was covered with innumerable hairs broken just below the level of the scalp, producing the typical black-dot ringworm. She was again treated for six months with various applications but to no avail. This patient was then sent to New York City for her second epilation with x-rays. There was a repetition of a complete epilation of the unaffected hairs with the diseased stubby, broken hairs holding tenaciously to the follicles. These could not be removed by traction with adhesive tape.

A nurse then spent one hour each day, five days a week, for four months manually pulling these diseased stubs with tweezers or literally digging them out with a sharp-pointed scalpel. At the end of this period the patient was apparently well, and there was a complete regrowth of hair. Today, some two years later, there is no evidence of the former ringworm infection.

This case proves that it takes a relatively large dose of x-ray irradiation to cause epilation of the diseased hairs, but it also shows that a 58-year-old woman can be epilated twice within six months with a complete regrowth of hair.

DR. CLARENCE S. LIVINGOOD, Galveston, Texas: This outstanding paper is on a subject which is most timely, because, in Texas at least, tinea capitis due to T. tonsurans is becoming more important each day. In my opinion, this paper, which is in reality a complete monograph on tinea capitis in the adult, will be referred to by all of us for years to come.

It is possible that endothrix infections of the scalp will become one of the most important public health problems in the Southwest. Currently, about 70% of all the infections of the scalp which my associates and I see at the John Sealy Hospital, of the University of Texas Medical Branch, Galveston, are due to an endothrix infection. Most of our patients have been children, but careful examination of all adult contacts of the infected children has resulted in the discovery of an increasing number of infected adults.

In a preliminary school survey study conducted by Dr. Ida Walton of my department, the results were as follows: 13% of 113 Negro children in one school, 3.7% of 146 Negro children in another school, and 1.7% of 610 white children had endothrix infections of the scalp. It seems probable that at least 500 or 600 children and adults in Galveston County, Texas, have an endothrix infection of the scalp.

It seems appropriate that there is a higher incidence of endothrix infection of the scalp in Texas. In the first place, this state is adjacent to Mexico, where there has been a very high incidence of endothrix infections of the scalp for many years, and in the second place, as all of you know, in Texas everything is bigger and better.

DR. LESLIE M. SMITH, El Paso, Texas: I am sure that Dr. Pipkin's excellent paper is going to make us all more conscious of the possibility of ringworm in many conditions that are not clinically typical of this infection in the scalps of both children and adults. Although I live in the same state as Dr. Pipkin, El Paso is 600 miles (96 km.) west of San Antonio in an entirely different climate, and differences are noted in the proportions of cases of scalp ringworm caused by the various organisms. This area has not participated in the epidemic of ringworm due to M. audouini. About 85% of my cases show the animal type of Microsporum. I find an occasional case due to M. audouini and a few due to the T. tonsurans group and to other species of Trichophyton.

DR. GEORGE M. LEWIS, New York: This paper appeals to me as a record of good observation and persistent effort extending over a long period. Dr. Pipkin kindly afforded me the opportunity of studying his presentation. There are several findings that may be emphasized. The distribution of tinea capitis due to the endothrix Trichophyton indicates a localization to several parts of the country different from that of other varieties. The number of cases in New York is not numerous and has not shown an increase during recent months.The clinical manifestations are often typical, and frequently the cultural findings are a surprise. It may be reiterated that filtered ultraviolet radiation (Wood light) is not reliable in diagnosing these infections, nor can this modality be used as a screening device if the presence of the endothrix Trichophyton is suspected. It is of considerable interest that Dr. Pipkin observed that the results of Wood light examination are positive in gray-haired persons, whereas they are negative in patients with dark hair. Since it is known that all fungi exhibit fluorescence and that with some endothrix trichophytons, such as that causing favus, this can be detected with the naked eye, there are two postulates that appear of interest: 1. If adequate fungous material were present, fluorescence would be present at all times and for all fungi. 2. With sparse amounts of fungous material (as commonly observed in infections due to T. sulfureum) the fluorescent effects may be observed only under ideal conditions (i. e., in gray hair). So far as treatment is concerned, my experience is similar to that of Dr. Shelmire, namely, that manual epilation is often required in addition to roentgen epilation and local applications before a cure is obtained. At best, these infections are difficult to eradicate.

DR. JAMES HERBERT MITCHELL, Chicago: Some of you may be aware of the fact that I have been much interested in Microsporum infections of the scalp. I made an extensive survey, the results of which appeared in the January, 1948, number of *The Medical Clinics of North America*, page 283. This survey showed the course the epidemic had taken and also the fact that I had seen and treated hundreds of patients. The point of interest to me in this paper is the small number of M. audouini cases. T. tonsurans infections and favus are no respectors of age. I have groups in which three and four generations are represented, and so far as the adult is concerned I am not particularly interested. However, I much appreciate this valuable

contribution. Among the hundreds of cases my colleagues and I saw in Chicago, and Chicago has had an estimated 30,000 cases, I saw in my private practice only one woman, 35 years of age, who was the mother of an infected child and who had a typical lesion in the scalp. A positive culture of M. audouini was obtained. I examined routinely the scalps of the mothers of infected children, and, if I didn't find other cases, I don't believe it was because of neglect. I have seen one other case which was demonstrated at a meeting of the Chicago Dermatological Society by Dr. Zakon. Aside from the woman aged 35 years, the oldest patient in my experience was a boy of 14 with rather extensive infection in the scalp. Because he had reached puberty, I gave him merely a topical application. At the age of 15 his scalp was entirely clear.

DR. ARTURO L. CARRION, San Juan, Puerto Rico: This paper should be a fundamental lesson to all of us. We usually think of ringworm of the scalp as something very extraordinary. Dr. Pipkin has emphasized the fact that such infections do occur and, most probably, are not as rare as is usually thought. I remember distinctly a young lady whose scalp showed several bald areas strongly suggestive of alopecia areata. From her age, the possibility of ringworm would have been excluded. Yet a close clinical examination and laboratory studies disclosed the fungous nature of the disease. It is worth while noting, further, that the fungus species found by Dr. Pipkin in Texas may produce in some instances only a diffuse thinning of the hair with almost imperceptible or no apparent scaling. The occurrence of this unusual clinical picture should be borne in mind, as it may be another misleading factor in adult infections. Failure to recognize these facts may lead to serious diagnostic errors which would be detrimental to prognosis, treatment, and epidemiology.

From the viewpoint of mycology it is interesting to know that the offensive organism in the region where Dr. Pipkin conducted his studies has been classed as T. tonsurans and not M. audouini, which is responsible for so many stubborn scalp infections in other parts of the country. This, however, is no compliment to the state of Texas, since the treatment problem in T. tonsurans infections of the scalp is as difficult as that in the cases produced by M. audouini. In Puerto Rico, where I have had the opportunity to study ringworm of the scalp for many years, about 50% of the infections are due to T. tonsurans, and, by hard experience, I have learned how difficult it may be to eradicate the disease in many of these cases.

I want to emphasize the advisability of observations on the microscopic morphology of the fungi isolated from cases of ringworm of the scalp. It is well known that the proper classification of the infecting organism is essentially important from the viewpoint of prognosis and treatment, and the chances of error are greatly reduced when the fungi are identified according to microscopic morphology rather than gross cultural characteristics.

DR. M. J. COSTELLO, New York: I should like to inquire of Dr. Pipkin whether he epilated the remaining hairs of the scalp infected with fungi and not removed with x-rays by inserting the fine needle of the short-wave high-frequency current. Often a child may be kept out of school because of a dozen hairs which remain after roentgen-ray epilation. This method is applicable not only to hairs that fluoresce, which may thus be removed by the above modality with the visual aid of the Wood light, but to nonfluorescent fungous-infected hairs, which may be epilated in a similar manner under ordinary light. Great difficulty is encountered in removing these infected hairs by manual epilation with tweezers. This problem in epilation is overcome in the above manner. When the current is turned on, and as the needle is withdrawn, the entire infected hair is often attached to it. The epilation is usually temporary (Costello, M. J.: ARCH. DERMAT. & SYPH. **54**:210 [Aug.] 1946). This procedure may help return the child to school in a much shorter time than would be possible otherwise.

DR. C. F. LEHMANN, San Antonio, Texas: A feature of some of the noninflammatory infections of the adult that has not been particularly stressed in the literature occurs in those due to the T. tonsurans organisms. I refer to the infections that present either (1) alopecia in small irregularly outlined linear patches with very sparse black dots or (2) late scarring simulating quiescent lupus erythematosus, pseudopelade, or cicatrizing alopecia. A diligent search for the fungus in such cases will most probably establish a specific causation when otherwise the condition would be put down as idiopathic.

Whether these infections in the adult scalp could be explained by endocrine influences changing the "soil" so that the organism can grow in it is an open question. However, I believe that there is no basis for such a premise, the reason being that most of the adults were normal

physiologically, as manifested by child-bearing, general good health, and normal menstrual cycles. Furthermore, three women were treated for several months with estrogenic substances locally and parenterally.

I should also like to call your attention to the epidemiologic survey that was made in this study. Three M. lanosum infections in the adult and two in the late adolescent were traced to kittens; one M. audouini infection in the adult was traced to a child. Of the T. tonsurans infections, 10 were traced to other members of the household; 6 infections in the adult were obtained from fingernail infections in beauty operators. We are particularly puzzled regarding the natural habitat of the T. tonsurans group. As yet, we have not traced any of the group to an animal.

This paper stresses in detail the importance of the removal of all infected stubs of hair, which in many instances involves careful, persistent, continuous care by the physician. Some of the stubs are so embedded in the skin that only by drastic measures, such as the application of phenol or blistering with cryotherapy, could they be extruded.

I should like to emphasize, as the paper states, that the newer proprietary fungicides which have been lauded by the manufacturers have been very disappointing in the treatment of this group of noninflammatory Trichophyton infections. It is in these conditions that so-called fungicidal preparations should be tested, and not in the cases in which the infected stubs loosen readily.

Dermatologists should not endorse any new commercial venture that offers to the general physician a "new fungicidal preparation for ringworm of the scalp" until it has been adequately tested clinically.

Dr. Stephen Rothman, Chicago: M. audouini is more sensitive to the fungistatic action of fatty acids than any other pathogenic species is. This high sensitivity explains the clearing of M. audouini infections of the scalp during puberty and the immunity of the adult scalp to this infection. Other mycotic scalp infections may occur in any age group. The amount of free fatty acids in the hair fat increases considerably with the advent of puberty. This increase suffices to hinder the "take" of M. audouini but not that of other pathogenic fungi.

Dr. James Lewis Pipkin, San Antonio, Texas: I remember Dr. Costello's article well, but we have been so busy picking and digging that we have not used his method. I want to thank Dr. Costello very much for citing this method. I am glad that so much interest has been shown in this reputedly very rare disease.

ERYTHEMA MULTIFORME FOLLOWING DEEP X-RAY THERAPY

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LOCALIZED primary radiation dermatitis resulting from deep x-ray therapy is commonly known, as is the eczematoid dermatitis that sometimes occurs in and about the irradiated site. However, a generalized cutaneous reaction due to radiotherapy, appearing distant to the portal of irradiation, is not well known. Consequently there is a dearth of information on this subject.

In 1903, Holzknecht, the famous Viennese radiologist, reported generalized cutaneous reactions following single large doses of superficial x-rays sufficient to produce moderately severe localized x-ray dermatitis. Since then, sporadic reports have appeared in the dermatological and radiological literature by Epstein,[1] Schreiner,[2] Kautzky,[3] Pardo-Castello,[4] Bray,[5] Moore,[6] Maccagno,[7] Castigliano,[8] Hopkins,[9] and, more recently, Arnold.[10]

The reaction which may follow deep x-ray therapy consists of a definite symptom complex with characteristic clinical and laboratory features. A generalized rash may appear within 2 to 21 days after deep x-ray therapy, usually administered for a cancerous tumor. It is frequently associated with fever and other constitutional symptoms which require several days to a month for abatement.

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Read before the Section of Dermatology and Syphilology at the 100th Annual Session of the American Medical Association, Atlantic City, N. J., June 15, 1951.

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TABLE 1.—*Analysis of Thirty-Two Reported Cases of Erythema Multiforme Due to X-Ray Therapy*

Series	No. of Cases	Condition for Which Treated	X-Ray Dosage	Prodromal Period, Days	Type of Eruption	Symptoms	Laboratory Findings	Duration, Days
Holzknecht	5	Facial hirsutism, psoriasis, favus	Mild erythema	28	Generalized or universal erythema, papular, scarlitiniform, papulo-vesicular	Pruritus, fever	.....	Several days to several weeks
Epstein	1	Cancer of uterus	Deep	3	Generalized purpura	Rheumatic pains, fever	.....	14; died, 42 days
Schreiner	1	Thyroid	Deep	12	Universal lichen ruber planus	Generalized pruritus	.....	.....
		Lumbar region	Deep, repeated	10	Universal lichen ruber planus	.....	.....	.....
Pardo-Castello	4	Cancer of mouth (2) testicle; post-operative cancer of stomach	Deep	2	Mormilliform, generalized erythema, edematous papular	.....	.....	2
Moore	1	Postoperative cancer of breast	Deep	..	Generalized angioneurotic edema	.....	.....	.....
Maccagno	1	Mediastinal lymphoblastoma	Deep	4	Generalized bullae	.....	.....	17
			Deep, repeated	3	Generalized bullae	.....	.....	3
Castigliano	1	Carcinoma uterus	Intra-uterine radium	..	Universal scarlitiniform	Fever, radiation sickness	.....	.....
Bray	7	Cancer of breast, ovary, cervix; ovarian cyst; thyrotoxicoses hypogonadism	Deep, 1,200-1,600 r	3-5	Generalized papuloedema	.....	.....	6-7
Hopkins	1	Metastatic cancer of skin	Deep, 6,000 r, 3 ports	20th day of treatment	Generalized erythema, petechiae, purpura	Fever, tachycardia, joint pains, radiation sickness	Leucopenia	24
Arnold	3	Seminoma	Deep, 1,200 r	4	Generalized bullae (iris), involvement mucous membrane	Fever	.....	15
		Cancer of urethra	8,000 r, 4 ports	12	Generalized papular erythema	Pruritus	.....	28
		Postoperative cancer of breast	6,000 r, 3 ports	6	Generalized deep-seated papules	None	.....	21
Kautzky	3	Cancer of cervix	180 kv., 1,100 r	5	Erythematous papular	Fever	.....	21
		Hyperthyrodism	150 r, 4 ports	28	Generalized urticaria	.....	.....	8
		Hemolytic jaundice	50 r, 3 ports	21	Generalized erythema, pigmentation	.....	.....	3 mo.
Loewe and Camiel	4	Cancer of tongue	200 kv., 4,800 r, 3 ports	18	Generalized erythema, bullous hemorrhagic eruption of face	Fever, acutely ill	Negative blood culture, eosinophilia	14
		Cancer of pharynx	2,400 r, 2 ports	8	Generalized maculo-papular, ulceration oral mucosa	Headache, nausea, fever	Negative blood culture, eosinophilia, occasional WBC and RBC in urine	21
		Cancer of cheek	8,000 r, 3 ports	10	Generalized papular erythema, hemorrhagic bullae, ulceration oral mucosa	Fever, nausea	Negative blood culture, eosinophilia, occasional WBC and RBC in urine	.....
		Cancer of palate	3,200 r, 4 ports	..	Generalized scarlitiniform	Fever, toxic	Negative blood culture, eosinophilia, 2+ albumin, occasional WBC and RBC in urine	13

The eruption may assume various forms, i. e., erythematous, papular, papulovesicular, lichenoid, bullous, scarlitiniform, purpuric, morbilliform, and exfoliative. Constitutional symptoms accompanying the cutaneous eruption include joint pains, fever, nausea and vomiting, tachycardia, prostration, weakness, pruritus, and radiation sickness. Eosinophilia, leukopenia, and mild kidney damage have been observed in some cases. Microscopic examination of the skin of an early lesion shows acute inflammatory edema, vascular congestion, diffuse polymorphonuclear-leucocytic infiltration of the corium, and an overlying parakeratotic layer.[11]

This syndrome is frequently misdiagnosed as some type of drug allergy, intercurrent infection, or infectious exanthema. The similarity of an erythema-multiforme type of reaction produced by deep x-ray and that due to the agents mentioned, and the lack of sufficient proof of x-rays as the causative agent, have been responsible for the reluctance to accept this condition as a definite entity. The difficulty involved in reproducing such a cutaneous reaction by repetition of the x-ray exposure of the same patient is apparent.

Over the past several years, we have had the opportunity to observe five private patients having typical erythema multiforme following deep x-ray therapy for various cancerous neoplasms. In two of these patients, whose cases are reported below, we were able to reproduce the condition by reexposure to x-rays, and thus give credence to the syndrome.

REPORT OF CASES

CASE 1.—L. S., a 53-year-old white man, was admitted to the hospital, where an exploratory laparotomy was performed on Dec. 22, 1950. A diagnosis of retroperitoneal lymphosarcoma was confirmed by pathological examination of retroperitoneal nodes removed at operation. Deep x-ray therapy was instituted postoperatively on Jan. 5, 1951. One million kilowatts was employed, and 300 r daily was administered to the abdomen, alternating between anterior and posterior fields. A total dose of 2,400 r to each port was administered, and the first course of deep therapy was completed Jan. 16, 1951. On the fifth day of treatment, there was a first-degree erythema over the treated port of the abdomen with extension of a fine macular rash beyond the treated port. Three days after completion of the first eight days of x-ray therapy, a temperature of 104 F. suddenly developed in the patient. Examination revealed a diffuse generalized papular erythema with marked edema of the extremities. The mucous membranes of the nose and mouth were similarly involved by an intense erythema. The patient complained of weakness, toxicity, and generalized pruritus. The white blood cell count showed a marked leucopenia of 1,500 white blood cells with 15% eosinophiles in an otherwise normal differential blood picture. The patient had been referred with the possible diagnosis of a delayed penicillin reaction or dermatitis medicamentosa. He had received several injections of penicillin three weeks previously. Drugs which had been prescribed included phenobarbital, dimenhydrinate (dramamine®), pyridoxine, and codeine. A dermatological diagnosis of erythema multiforme was made. The patient was given 10 mg. of methapyrilene (histadyl®) hydrochloride intramuscularly, and the erythema blanched temporarily after a short time. The use of all other drugs was discontinued, and 1 cc. of methapyrilene hydrochloride was administered intramuscularly every four hours. Within 24 hours the rash notably subsided, the pruritus disappeared, and the temperature dropped to normal. After several days, with complete involution of the papular edema, the skin assumed a smooth bronze color which cleared in 10 days, accompanied by a gradual elevation in the white blood cell count to normal.

In order to eliminate the possible drug origin, the patient was allowed to resume one by one the use of all the drugs that he had been receiving previously, without recurrence of the rash. Since the seriousness of the diagnosis warranted continuation of deep x-ray therapy despite his

11. Loewe, L., and Camiel, M. R.: Exanthem Complicating Neoplastic Disease, Am. J. Roentgenol. **43**:587, 1940.

previous reaction following irradiation, he was again treated with 1,000,000 kv., receiving 300 r to the abdomen on Feb. 2, 1951. Twenty-four hours later there appeared a fine generalized macular rash. This subsided within three days upon administration of methapyrilene hydrochloride intramuscularly. Following this episode, deep therapy was continued in conjunction with premedication of 100 mg. of pyrilamine maleate (neo-antergan®) followed by 1 cc. of methapyrilene hydrochloride intramuscularly after each treatment and 50 mg. of pyrilamine maleate four times a day. On this routine, x-ray therapy was completed without initiation of further eruption, and there was excellent response of the tumor to irradiation.

Case 2.—B. R., a 45-year-old white woman, had a radical mastectomy for carcinoma of the right breast. She received deep x-ray therapy postoperatively to two ports. With high-voltage (200 kv.) x-ray therapy to the axillary field and low-voltage (120 kv.) therapy to the anterior chest wall, 300 r was given daily, alternating between these portals until a dose of 1,500 r was given to each. Ten days after termination of therapy the patient manifested a diffuse acute

Generalized erythematous papuloedema 11 days after institution of high-voltage x-ray therapy (1,000,000 kv.) to an abdominal port (Case 1).

erythema over the left side of the upper chest, shoulder, neck, and face, associated with mild pruritus. The local reaction at the two ports of treatment demonstrated the usual primary radiation reaction following deep therapy. The patient had received no oral medications. A diagnosis was made of erythema multiforme due to x-rays. Mild local applications were applied. At the end of five weeks the erythema had completely subsided.

Case 3.—L. M., a 55-year-old white Argentine man, was given deep x-ray therapy for bronchogenic carcinoma, 1,000,000 kv. being employed. He was given a total of 4,000 r to each of two ports on the chest, anteriorly and posteriorly. Treatment was instituted on Aug. 4 and completed on Aug. 16, 1949. One day after completion of treatment, a generalized scarlitiniform rash appeared over the body. The temperature was normal, and the rash was asymptomatic. There was no change in the skin at the treated ports. The patient was taking no oral medications. General physical examination disclosed no abnormalities except for the rash. A diagnosis of erythema multiforme due to deep x-ray treatment was made. The patient was treated with tripelennamine (pyribenzamine®) hydrochloride, 50 mg. four times a day. In 24 hours the eruption was involuting, and in three days it had disappeared entirely.

CASE 4.—M. S., a 48-year-old white woman, was given postoperative deep x-ray therapy following a radical mastectomy for carcinoma of the right breast. With high-voltage (200 kv.) x-ray therapy to the axillary field and low-voltage (120 kv.) therapy to the anterior chest wall, 300 r was given daily, alternating between these ports until a dose of 1,500 r was given to each port. On the third day after completion of the x-ray therapy, a generalized morbilliform rash and a temperature of 101 F. developed. There were no complaints except for a mild generalized pruritus. The patient was receiving no oral medication. A tentative diagnosis of measles was made by the family physician. A general physical examination was noncontributory. There was no regional adenitis, and no Koplik spots had been observed. The patient gave a history of having measles in childhood. The white blood cell count was normal. A diagnosis was made of erythema multiforme due to x-rays. The patient received bland local treatment. In 72 hours the rash disappeared completely. A week after the episode the patient exhibited a mild alopecia. Hair growth returned to normal after an interval of several months.

CASE 5.—F. P., a 33-year-old white woman, was admitted to the hospital with an enormous abdomen distended by a diffuse myosarcomatosis. She received 300 r daily through a 1-cu.mm. filter to two abdominal ports, 200 kv. being employed. At the completion of the course of deep x-ray therapy she had received 5,400 r. Five days later a generalized maculopapular rash developed, with a white blood cell count of 2,000 and an eosinophile count of 31%. The patient had not been taking any oral medication. A diagnosis was made of erythema multiforme resulting from the deep x-ray therapy. The rash continued to spread and in some areas became confluent. There was a mild pruritus but no toxic symptoms. Local medication was administered. The rash slowly faded over the next three weeks, with return of the blood cell count to normal. The skin was clear at the end of one month. The patient lost 30 lbs. (13.6 kg) owing to the resolution of the extensive abdominal mass, and the abdomen assumed its original contour.

The patient was entirely asymptomatic until she was reexamined four years later because of uterine hemorrhages, apparently due to a small intramural leiomyoma. At this time an intrauterine tandem of radium capsules was inserted, and the patient received a dose of 2,000 mc.-hr. Eight days later a profuse generalized macular rash developed similar to that which had been observed following deep x-ray therapy to the abdomen four years previously. She had chills and temperature of 104 F., with generalized toxicity evidenced by nausea and vomiting. The extremities became markedly edematous. No oral medication had been administered. Findings from laboratory examinations were as follows: white blood cells, 2,500, with 8 eosinophiles and an otherwise normal differential count, and red blood cells, 3,000,000, with 60% hemoglobin. There was albumin in the urine (1+) on repeated occasions after an absence of albumin in the urine at the initial examination. Repeated blood cultures were negative. At the end of two weeks a generalized exfoliation developed. This slowly subsided under mild local medication, and the patient was discharged from the hospital at the end of three weeks. Six weeks after the onset of symptoms the skin had returned to normal. There has been no recurrence of the neoplasm, which readily resolved following the intrauterine radium implants.

COMMENT

Our 5 cases, analyzed in Table 2, appear quite representative of this syndrome following x-ray therapy and assumed much the same pattern as the 32 cases selected from the literature and analyzed in Table 1. The cutaneous manifestations included papuloerythema with edema, generalized macular erythema with exfoliation, and scarlitiniform and morbilliform eruptions. Constitutional symptoms were manifested by nausea, vomiting, and extreme toxicity in one patient (Case 5), and temperatures of 104 F. in two patients (Cases 1 and 5). Mild kidney damage was observed in the patient in case 5. Both of these patients had marked leucopenia and eosinophilia. The other three cases represent milder manifestations that may also occur in this type of x-ray reaction.

There was no clinical or laboratory evidence of infection in any of these patients. All possibility that allergies, drug reactions, and acute infectious exanthems were causative factors was carefully eliminated.

Other investigators have reported the absence of leukocytosis and repeated negative blood cultures as evidence against an infectious origin. The extreme leukopenia present in the patient in Case 1 is further confirmation of a massive constitutional reaction to irradiation that is known to follow deep x-ray therapy in some instances.

Drug allergy as an etiologic agent in Case 1 was ruled out before the opportunity presented itself for reproducing the eruption. The patient had been taking phenobarbital, 0.5 grains nightly, for years. Pyrodoxine, dimenhydrinate, and codeine had been prescribed recently. The use of all these drugs was temporarily discontinued and then they were administered separately for several days without a recurrence of the rash. The patient then continued the use of all medications without further difficulty.

TABLE 2.—*Analysis of Five Cases Observed of Erythema Multiforme Following X-Ray Therapy*

Case, No.	Condition for Which Treated	X-Ray Dosage	Prodromal Period, Days	Type of Eruption	Symptoms	Laboratory Findings	Duration, Days
1	Retroperitoneal lymphosarcoma	1,000,000 kv., 300 r daily, 4,800 r (2 ports)	5th day of therapy	Generalized papular erythema and edema, congestion of mucous membranes of mouth and nose	Generalized pruritus, toxic, fever	WBC, 1,500; eosinophiles, 15	18
1	Retroperitoneal lymphosarcoma	1,000,000 kv., 300 r daily (2 ports)	2d day of therapy	Generalized macular	.....	WBC, 3,500	3
2	Postoperative cancer of breast	200 kv. unfiltered, 3,000 r (2 ports), 300 r daily	10	Generalized erythema	Pruritus	.....	35
3	Bronchogenic carcinoma	1,000,000 kv., 6,000 r (2 ports)	13	Generalized scarlatiniform	None	.....	3
4	Postoperative cancer of breast	200 kv. unfiltered, 3,000 r (2 ports), 300 r daily	9	Generalized morbilliform	Pruritus, alopecia	.....	3
5	Diffuse peritoneal sarcomatosis	1,200 kv., 5,400 r	5	Generalized maculopapular	Pruritus	WBC, 2,000 eosinophiles, 31	30
5	Leiomyoma uterus	Intrauterine radium, 2,000 mc.-hr.	8	Generalized macular with general exfoliative dermatitis	Chills, fever, nausea, vomiting	WBC, 2,500; hemoglobin, 60%; eosinophiles, 8; RBC, 3,000,000; albumin, 1+; blood culture, negative	42

In two patients (Cases 1 and 5) the rash was reproduced, after an interval of several weeks in the former and after four years in the latter, when radiotherapy was repeated. In the first patient (Case 5) radium implants of 2,000 mc.-hr. in the uterus were followed by a rash and fever similar to that which had occurred following deep x-ray therapy to the uterus four years previously. In the second patient (Case 1) deep x-ray treatment produced the rash and fever in both instances. Schreiner,[2] and Maccagno [7] were also able to reproduce the cutaneous reaction in two patients by repeating deep x-ray irradiation (Table 1). These four cases, Cases 1 and 5 of our own and two cases in the literature, seem to offer strong evidence in favor of establishing irradiation as the etiologic agent in the production of this syndrome.

One change which results from the action of irradiation on tissue is that of cellular decomposition. Radiation sickness is the chief generalized manifestation

of primary tissue damage. It would seem logical that an agent capable of instituting this type of response could reasonably account for the radiation syndrome that has been described. We believe with Artz and Fuhs [12] that this syndrome results from absorption of the products of cellular degeneration, probably protein disintegration of tumor tissue and of normal tissue as well. The eosinophilia observed in many of these patients would suggest a protein breakdown. The response to antihistamines might indicate some type of allergic reaction, but more likely it indicates the production, as a result of the tissue response to deep irradiation, of large amounts of histamine, a product considered by some to play a part in the mechanism of radiation sickness.

It has been our experience that in patients manifesting this type of reaction to x-rays or radium there is very often an excellent clinical response of the involved tumor to x-ray therapy. Enfield,[13] likewise, stated that the toxic erythemas occurring as a complication of irradiation were due to the rapid destruction of a radiosensitive tumor.

Exanthems occurring in association with the administration of radiotherapy are, in certain instances, on the basis of drug or other sensitivity or due to infection of bacterial or virus origin. However, when these causes have been duly eliminated, the possibility of an erythema multiforme due to irradiation should be considered.

The clinical features of 5 cases of erythema multiforme due to x-rays have been added to 32 cases analyzed from the literature. In two of our patients, the exanthem was reproduced by repeating irradiation. Similarly two cases are noted in the literature in which evidence that erythema multiforme can be caused by local irradiation was given by reproduction of the rash through repetition of the x-ray exposure. Virus and bacterial infection and drug allergy were eliminated as possible etiologic agents. There is marked contrast in response to treatment and in shortening the course of the syndrome in those patients in whom antihistamines were administered as compared with those observed before the advent of this drug.

CONCLUSIONS

The clinical, pathological, and laboratory features of erythema multiforme due to deep x-ray therapy have been presented and analyzed, based on 32 cases collected from medical literature and 5 cases in which the patients were examined and treated by the authors. The following evidence has been given to establish this type of reaction due to local deep x-ray irradiation as a distinct entity:

1. A prodromal period occurred in each instance following deep x-ray therapy.

2. Radiation sickness or toxic constitutional symptoms were present in severe cases.

3. Eosinophilia, leukopenia, and mild kidney damage were demonstrated as evidence of massive x-ray effect.

4. The response of the syndrome to antihistamines and the ability of these drugs to inhibit the reaction were demonstrated.

5. Radiosensitivity of the tumors was apparent in many of those patients in whom the reaction occurred.

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12. Artz, L., and Fuhs, H.: Roentgen Rays in Dermatology, Baltimore, William Wood & Company, 1937.

13. Enfield, C. D.: Sequelae of Roentgen Therapy, Kentucky M. J. **35**:341, 1937.

6. The cutaneous reaction was reproduced experimentally in two of our own patients and in two patients whose cases are reported in the literature.

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ABSTRACT OF DISCUSSION

Dr. Robert N. Buchanan, Jr., Nashville, Tenn.: Dr. Davis and Dr. Pack, by reporting 5 additional cases and collecting 32 cases from the literature, have shown that a generalized cutaneous reaction due to radiation but distal to the site of administration does occur. Evidence that this response does occur seems established.

In two of the cases previously reported the usual method of proof, reproduction of the identical reaction by a second exhibition of the suspected cause, was observed. Dr. Davis and Dr. Pack reported two additional cases of reproduction following reexposure to high-voltage x-rays. The fact that only 37 cases showing this reaction have been reported clearly indicates its infrequency. I have never seen it, in spite of a fairly close association with patients receiving deep x-ray therapy for the various diseases commonly treated in this manner.

It is generally agreed that erythema multiforme can be caused by drugs, bacteria, injections (especially of sera), deep x-ray therapy, etc. Most frequently the cause is unknown. Hebra, in his original description, regarded the common form of the disease as a primary idiopathic recurrent condition. To this day nothing has been presented to refute this concept or to reveal the basic disturbance of the disease. Apparently it is due to some "noxious humor" which may be drugs, a toxin derived from a focus of infection, the action of deep x-rays on tissue, or other causes. Perhaps in time observations like these will reveal the true nature of the disturbance.

I should like to raise a question in nosology. According to my concept of erythema multiforme, only two of the patients reported upon today had erythema multiforme. If erythema multiforme includes any type of erythema, then all of these patients had erythema multiforme. The patient in Case 2 showed a diffuse acute patchy erythema; in Case 3 there was a generalized scarlitiniforme rash, and in Case 4 a generalized morbilliform rash. Would it not be better to regard these patients as showing a toxic erythema due to the effects of deep x-rays?

Dr. Jeff Davis, New York: As to the title of the paper, Dr. Pack and I discussed this beforehand. Many of the other authors who have written on this subject indicate this entity by erythema-multiforme type of reaction. My own conception of an erythema multiforme is a toxic generalized eruption on the skin produced by some type of toxin. Since we know that many agents of toxic nature can produce it, x-rays may well be included as such an agent.

I, however, would like to disagree with Dr. Buchanan in one respect. We do not believe that this condition is quite as rare as would be evidenced by the reports in the literature. We believe, on the contrary, that this is a definite entity and that it is being passed over by roentgenologists in particular and by dermatologists in general because of lack of knowledge of this type of eruption. Dermatologists do not have the opportunity to see many patients who have deep x-ray therapy, and the roentgenologists are disinclined to think that x-rays can produce any sort of noxious reaction other than the therapeutic effect for which it is given. We believe that if one is on the lookout for this type of eruption, one will find many more cases.

PEMPHIGUS VULGARIS

A Clinical and Laboratory Study

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A SERIES of laboratory studies were conducted on 19 patients with pemphigus vulgaris at the Dermatology Service of the University of Minnesota. Six of the patients were women and 13 were men. Eight were born in the United States, three in Sweden, two in Norway, one in Finland, and one in Russia. There was only one Jew, and he was American-born. The patients included two with acute pemphigus, one with pemphigus foliaceus, one with pemphigus vegetans, and one with pemphigus erythematosus. To date six have improved. There were six deaths in the group. The apparent prolongation of life expectancy in the others was discussed elsewhere.[1]

The laboratory findings are taken up separately. In the accompanying tables the blood levels of only a few of the patients are listed. This is done for clarification and in order to show principally those levels determined at comparable times for the same patients. In many instances, complete studies were not or could not be carried out for all the patients. The effort was to offer representative sampling of the entire group. The first consideration was given to changes produced on the cellular elements of the blood and blood-forming tissues. Most of the patients showed evidence of anemia during the course of their illness. The hemoglobin estimates ranged from 8 to 14.9 gm. per 100 cc. of blood. As the disease progressed, the anemia generally appeared during the severe and febrile phases and tended to parallel its course. In this series of patients the anemia became more profound with the accentuation of the febrile phase and as the toxemia increased. Even though there was no evidence of acute blood loss, the drop in hemoglobin concentration at times was very rapid. The picture was that of a normocytic anemia. All anemia patients were supported and benefited by transfusions from normal persons. In those patients who recovered, the anemia improved more slowly than did the skin. When improvement of the anemia occurred, it was attributable, however, not so much to the transfusions as to the decrease of the toxic state. Whatever the toxic factor may be in pemphigus, it exerts a strong effect on the red blood cells.

From the Division of Dermatology, University of Minnesota Medical School, Dr. Henry E. Michelson, Director.

Read before the Section on Dermatology and Syphilology at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 15, 1951.

1. Fisher, I.: Pemphigus, Bull. Staff Meet., Univ. Minn. Hosp. **19**:285, 1948.

RESULTS OF CELLULAR STUDIES

Bone marrow biopsies were performed for some of the patients, and a hyperplastic marrow was reported by the hematologist. It is possible that a hemolysis of red blood cells is the basis for the rapidly developing anemia, as two of the patients showed suggestive evidence of a hemolytic state. Studies of the reticulocyte count and quantitative erythrocyte protoporphyrin determinations did not offer supportive evidence for the hemolytic state. In two patients with increased fragility of the red corpuscles, the red blood cell volume and diameter were examined. The results indicated the presence of many spherocytes in the peripheral blood. There was no explanation for the change, nor did it seem of sufficient magnitude to aggravate the hemolytic state. The remaining bone marrow studies were reported simply as showing "no evidence of a primary blood disease." The bone marrow was hyperplastic. In some instances a toxic formula was reported. The eosinophilia of the peripheral blood was reflected in the bone marrow by a similar elevation of the eosinophiles. The eosinophiles in the peripheral blood of all the patients studied ranged from 4 to 23%. The same was true in the bone marrow. During much of the disease the eosinophile count ranged from 10 to 12%. In both the bone marrow and the peripheral blood many toxic neutrophiles were demonstrable. There were no cells in the bone marrow which resembled or were suggestive of those seen in acute lupus erythematosus.

The erythrocyte sedimentation rate in most instances showed the expected increase ranging from 60 to 120 mm. in 60 minutes. In one patient with severe pemphigus vulgaris of the vegetating type, the sedimentation rate was normal. On three later occasions the sedimentation rate was below normal in the same patient. I can offer no explanation for this phenomenon. In most instances the sedimentation rate increased as the body temperature rose and as the systemic symptoms became severe. With clinical improvement the sedimentation rate also returned to nearer normal. This was true of all patients who recovered from the more acute phase.

RESULTS OF LABORATORY STUDIES

The blood chemistry studies proved to be somewhat more informative. The blood urea nitrogen was elevated in six of the patients. It remained elevated or rose in three patients who died shortly after. In the others, the level soon returned to normal. At no time was there evidence of lasting renal impairment.

For five of the patients complete liver-function tests were performed. For each patient the tests included determinations of serum bilirubin, cephalin-cholesterol flocculation, sulfobromophthalein (bromsulphalein®) sodium retention, thymol turbidity, the urinary Ehrlich reaction, and urinary urobilinogen. There was no evidence of severe liver impairment at any time. Two patients had an elevated serum bilirubin level which returned to normal. Another patient showed a 15% retention of the sulfobromophthalein sodium dye in 45 minutes. This test gave normal results at a later examination.

Limited porphyrin studies were conducted on seven patients. The normal value for the excretion of urinary coproporphyrin is 30 to 100 γ per day. All seven of these patients exhibited abnormally high excretory values, as indicated in Table 1.

One patient, J. J., had an abnormally high urinary coproporphyrin excretory level. The determination was repeated on three separate occasions and was reported as showing 305, 292, and 344 γ per day. In Patient H. H., the urinary coproporphyrin was 170 γ in 24 hours. This estimation was made after the patient's skin

TABLE 1.—*Twenty-Four-Hour Coproporphyrin Excretion*

Patient	Type of Pemphigus	γ/Day
H. H.	Foliaceus	170
J. J.	Bullous	344
J. B.	Vegetating	272
I. E.	Bullous	303
M. P.	Bullous	328
M. W.	Bullous	713
H. T.	Bullous	370

TABLE 2.—*Sample of Results on Simultaneous Blood Chemistry Studies Done at Time of Admission*

Patient	Chlorides, Mg./100 Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Proteins, Gm./100 Cc.		Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.
			Albumin	Globulin		
M. G.	616	10-25	1.8	2.6	...	....
M. W.	609	10	2.4	2.2	325 (141)*	20.4 (5.3)
I. E.	628	8	4.2	2.2	345 (150)	13.5 (3.5)
H. N.	632	8	3.1	3.3	554 (144)	19.3 (5.0)
G. K.	530	15-38	4.0	1.7	...	....
A. L.	608	60-44	...	...	...	....
C. H.	624	35	...	...	341 (148)	14.6 (3.5)

* Numbers in parentheses indicate values in milliequivalents per liter.

TABLE 3.—*Comparative Chloride, Sodium, and Potassium Levels Determined on Same Date During an Active Phase of Pemphigus*

Patient	Chlorides, Mg./100 Cc.	Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.
I. E.	628	345 (150)*	13.5 (3.5)
M. P.	636	345 (150)	15.2 (3.9)
C. H.	624	341 (148)	14.6 (3.8)
I. B.	628	335 (145.6)	15.2 (3.9)
	630	340 (148)	17.6 (4.5)

* Numbers in parentheses indicate values in milliequivalents per liter.

had improved. The level of 713 γ of coproporphyrin per day in M. W. was the highest for the group. The course of the disease in this patient was a fulminating one resulting in early death. The significance of abnormal excretion of coproporphyrin in pemphigus is unknown.

Blood.—Soon after admission of each patient to the hospital a selected group of blood chemistry studies was done. Table 2 lists a sampling of results from this group of studies. The blood chloride level was depressed in one patient, and the blood urea

nitrogen was elevated in three. The serum sodium was well above 132 mEq. in the patients examined. In Table 3 is listed a group of blood chloride, sodium, and potassium levels determined simultaneously as a base line in another group of patients.

The serum sodium and potassium levels varied somewhat according to the patient's condition. All the sodium levels remained fairly high and ranged from 141 to 150 mEq. per liter. The greatest shift occurred in the chloride levels. In one patient, I. B., the blood sodium was 148 mEq. per liter (340 mg. per 100 cc.) early during the bullous phase of her disease, and the potassium level was 3.9 mEq. per liter (15.2 mg. per 100 cc.). In the same patient during the early vegetative phase, the sodium was reported as 141.2 mEq. per liter (325 mg. per 100 cc.) and the potassium as 3.9 mEq. per liter (15 mg. per 100 cc.). During the later vegetative phase both electrolyte levels rose. The sodium rose to 153 mEq. per liter (353 mg. per 100 cc.) and the potassium to 4.5 mEq. per liter (17.6 mg. per 100 cc.); see Table 4. The sodium and potassium levels could not be correlated with the chloride levels. The chloride levels shifted during the course of the illness, ranging from 630 to 568 mg. per 100 cc. without any relation to the condition of the patient. A single

TABLE 4.—*Sodium and Potassium Levels in One Patient (I. B.)* During Changing Picture of Her Disease*

Phase	Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.
Bullous	340 (148)†	15.2 (3.9)
Vegetative	325 (141.2)	15 (3.9)
Late vegetative	353 (153)	17.6 (4.5)

* Lesions remained in the vegetative stage for a long time, and the patient later died when the lesions were in a bullous phase. This patient was 32 years of age, the youngest in the group.
† Numbers in parentheses indicate values in milliequivalents per liter.

check of the vesicle fluid in this patient revealed a chloride level of 626 mg. when the blood chloride level was 568 mg. per 100 cc. four days later. The determinations of sodium and potassium in the vesicle fluid were unsatisfactory.

In only one fatal case were the blood chlorides reported at a low level. Two days prior to the patient's death, the blood chloride was reported as 530 mg. per 100 cc. On a previous occasion the level had been 616 mg. per 100 cc. In two other patients who had severe forms of pemphigus but who have survived, the levels when the disease was severe were reported as 556 and 568 mg. per 100 cc., respectively.

The instructive approach would be to check levels in the bullous fluid, blood, and spinal fluid at the same time. Specimens obtained simultaneously would best reflect the patient's condition at any one time and would perhaps shed light on the underlying pathology. Unfortunately, such a plan was not carried out. In one patient, O. M., the blood chloride level was 616 mg. per 100 cc. and the sodium level was 138 mEq. per liter, while the bullous fluid revealed 618 mg. per 100 cc. of chloride, with a sodium level of 139 mg. and a potassium level of 5.8 mg. per 100 cc. The spinal fluid chloride was reported as 756 mg. per 100 cc. on the same day. Tables 5 and 6 illustrate an attempt at comparison of levels.

Bullous Fluid.—The bullous fluid was examined in four patients. In one patient with pemphigus vegetans the chloride level in the fluid was examined and was

reported as 625 mg. per 100 cc., a level comparable with that in her blood. In the more recent patients of the reported group an effort was made to correlate the blood, bullous fluid, and excretory levels of the electrolytes. The levels in the bullous fluid paralleled those in the blood, as can be seen in Table 6. In no case was there a distinctive difference between the electrolyte value in the blood and that in the

TABLE 5.—*Comparative Simultaneous Levels of Salts and Proteins*

Patient	Chemical Values Combined			Proteins, Gm./100 Cc.	
	Chlorides, Mg./100 Cc.	Sodium, Mg./100 Cc.	Potassium, Mg./100 Cc.	Albumin	Globulin
V. C.	657	332 (144.4)*	20.2 (5.17)	4.0	2.5
J. J.	556	327 (144)	....	3.6	4.2
A. L.	626	...	....	4.0	4.0
H.	624	341 (148)	....	1.88	4.03
M. P.	636	345 (150)	15.2 (3.9)	3.6	3.0
I. B.	628	340 (148)	15.2 (3.9)	3.9	1.9

* Numbers in parentheses indicate values in milliequivalents per liter.

TABLE 6.—*Comparative Levels of Chloride, Sodium, and Potassium Obtained Simultaneously from Spinal Fluid, Vesicle Fluid, and Blood*

Patient	Chlorides, Mg./100 Cc. (Factor 5.8)	Sodium, Mg./100 Cc. (Factor 2.3)	Potassium, Mg./100 Cc. (Factor 3.85)
Blood			
I. B.	628	340	15.2
J. A. W.	631	310	17.8
V. C.	657	332 (144.4)*	20.2 (5.17)
O. M.	616	317.4 (138)	....
M. S.	638 (110)	294 (128)	18.48 (4.8)
M. P.	609 (105)	333.5 (145)	20.4 (5.3) 15.2 (3.9)
Spinal Fluid			
V. C.	729	...	....
O. M.	756	...	....
M. S.	736.6	345 (150)	13.29 (3.4)
Vesicle Fluid			
I. B.	625	...	....
J. A. W.	630	331	20
O. M.	618	319.7 (139)	22.3 (5.8)

* Numbers in parentheses indicate values in milliequivalents per liter.

bullous fluid. The parallel findings applied for sodium and potassium levels, as well as for the chlorides. This gives more credence to the thought that the fluid found in pemphigus bullae is a transudate.

Serum Protein.—An attempt was also made to evaluate the course of the disease by the serum protein values. As is shown in Table 7, there was a change in the albumin-globulin ratio similar to that reported by others. According to Lever, the serum albumin levels in pemphigus vulgaris chronicus and early in pemphigus vul-

garis acutus are only moderately lowered or are normal. Table 8 shows the return to a more normal value for serum protein as the patient's condition either became stationary or went into a remission. It was not possible to correlate the changing serum albumin values with the changing blood ion concentrations.

The levels of the serum protein varied considerably during the course of the patients' disease. In most patients the serum albumin values dropped while the globulin rose. This change occurred when the general process became severer. The increase in globulin was real as well as relative. The severity of the illness was indicated by the degree of cutaneous involvement, fever, anemia, and general evidence of toxicity. The severest picture can presumably be considered an acute exacerbation in a patient with chronic pemphigus vulgaris. Not all the patients died during the acute phase. In some the disease returned to a more chronic phase with

TABLE 7.—*Sample of Serum Protein Fractionation*

Patient	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Alpha Globulin, Gm./100 Cc.	Beta Globulin, Gm./100 Cc.	Gamma Globulin, Gm./100 Cc.
A. L.	6.25	2.6	3.58	1.06	0.68	1.84
I. H.	5.88	1.85	4.03	1.24	1.15	1.64
O. M.	5.4	2.5	2.9	1.0	0.8	1.0
A. G.	6.7	2.5	4.2	1.3	1.0	1.9
H. T.	5.5	1.3	4.2	1.5	1.1	1.6
Normal values*	6.5-8.1	3.6-5.6	2.5-3.3	0.6-1.7	0.4-1.4	0.6-1.4

* Normal albumin-globulin ratio is 1.2 to 1.8.

TABLE 8.—*Protein Levels in Patient with Pemphigus Foliaceus (H. H.)*

Date		Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.
9/29	Pemphigus vegetans	6.1	3.1	3.0
10/21	Pemphigus foliaceus	5.9	2.9	3.0
11/19	Pemphigus foliaceus	6.2	3.2	3.0
12/15	Pemphigus foliaceus	7.0	2.2	4.8
1/12	Deep thrombophlebitis with rubor; normal results on liver-function tests	6.6	3.7	2.9

only a few pemphigus bullae. In others the disease apparently went into complete remission, and all evidence of pemphigus disappeared. In several there has been no recurrence after two years. As the patient's disease became less severe, the serum albumin began to rise to a more normal level and the globulin fell proportionately. I do not understand the meaning of this change but can only point out that the changes which occurred in the globulin were in the gamma fraction.

The method for determining the serum protein values as listed in this paper is one utilized at the University of Minnesota Hospitals.[2] This method for fraction-

2. Jager, B. V., and Nickerson, M.: Simple Quantitative Chemical Method for Estimating Globulin in Human Serum, J. Biol. Chem. **173**:683, 1948. Majoor, C. L. H.: Possibility of Detecting Individual Proteins in Blood Serum by Differentiation of Solubility Curves in Concentrated Sodium Sulfate Solutions, Yale J. Biol. & Med. **18**:419, 1946; Possibility of Detecting Individual Proteins in Blood Serum by Differentiation of Solubility Curves in Concentrated Sodium Sulfate Solutions: Comparison of Solubility Curves with Results of Electrophoresis Experiments, J. Biol. Chem. **169**:583, 1947. Weichselbaum, T. E.: Accurate and Rapid Method for Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path. **10**:40, 1946.

ating the serum proteins is based on differential precipitation with salts. Albumin is determined after precipitation of all the globulins with 26% sodium sulfate solution. This procedure gives values for albumin which are in much closer agreement with those for albumin determined electrophoretically than are the values found by the older method of Howe in which 21.5% sodium sulfate solution was used.[3] Further fractionation with 19% sodium sulfate solution permits the determination of a fraction which is quantitatively comparable with the electrophoretic alpha globulin fraction. The fraction that is precipitated by one-third saturation with ammonium sulfate gives a component which is closely related quantitatively to gamma globulin. The arithmetical difference between the value for total globulin and that for alpha plus gamma globulin is called the beta globulin value.

In recent articles Lever has reported values for the protein content of serum and blister fluid as determined by electrophoretic analysis.[4] The present report cannot be accurately compared with his because the methods vary. The comparison of percentage distribution of euglobulin, pseudoglobulin, and albumin determined by the "salting-out" technique with that of alpha, beta, and gamma globulins and

TABLE 9.—*Serum Protein Fractionation in Patients with Dermatitis Herpetiformis*

Patient	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Alpha Globulin, Gm./100 Cc.	Beta Globulin, Gm./100 Cc.	Gamma Globulin, Gm./100 Cc.
J. M.	7.9	4.6	3.3	1.2	1.2	0.9
T. L. B.	7.6	4.4	3.2	1.4	0.7	1.1
R. V. 5/17	7.1	3.5	3.6	1.5	1.1	1.0
6/12	7.6	4.2	3.4	1.3	1.2	0.9
C. R.	7.0	3.5	3.5	1.2	0.6	1.7
W. W.	7.4	4.0	3.4	1.3	1.1	1.0

albumin as shown on the electrophoresis experiments reveals a fair degree of correlation between the two methods of analysis.[5]

Table 7 gives a number of values for serum proteins as fractionated in order to give a picture comparable with the curve obtained by electrophoretic analysis. In this instance the values were determined by the "salting-out" technique, as discussed earlier. It is not possible by this method to fractionate the serum proteins and obtain values for $alpha_1$, $alpha_2$, $beta_1$, and $beta_2$ globulin as is done by electrophoresis. However, the values for alpha, beta, and gamma globulin as obtained by this method show a fair degree of correlation with those obtained on electrophoresis experiments.

A study of the serum proteins in H. H., a patient with pemphigus foliaceus, shows what happened to these blood values at various times. Early in the bullous

3. Milne, J.: Serum Protein Fractionation: Comparison of Sodium Sulfate Precipitation and Electrophoresis, J. Biol. Chem. **169**:595, 1947. Petermann, M. L.; Young, N. F., and Hogness, K. R.: Comparison of Howe and Electrophoretic Methods for Determination of Plasma Albumin, ibid. **169**:379, 1947.

4. Lever, W. F.: The Proteins in Pemphigus Vulgaris: I. Electrophoretic Analysis of the Proteins in the Blood Serum of Patients with Pemphigus Vulgaris, J. Invest. Dermat. **14**:205, 1950; II. Electrophoretic Analysis of the Proteins in the Blister Fluid of Patients with Pemphigus Vulgaris, ibid. **14**:219, 1950.

5. Dole, V. P.: The Electrophoretic Patterns of Normal Plasma, J. Clin. Invest. **23**:708, 1944. Stern, K. G., and Reiner, M.: Electrophoresis in Medicine, Yale J. Biol. & Med. **19**:67, 1946.

phase the serum albumin and globulin values were in a 1 : 1 ratio. As the disease progressed there was a drop in the serum albumin, with a change of the albumin-globulin ratio. During a later part of the patient's illness, after the exfoliative stage had been well established, the serum albumin value was found to be less than half the globulin value. At this point the patient was very ill, had a high fever, and presented generalized edema. Just prior to discharge, when the patient had improved considerably, the albumin value had increased again (Table 8). For comparison it was decided to determine values for the serum protein in patients during the active phase or exacerbation of dermatitis herpetiformis. No gross abnormalities could be detected (Table 9).

I have previously assumed that the maintenance of proper levels was a significant factor in prolonging the life expectancy and lowering the morbidity of pemphigus patients. There has long been the feeling that poor nitrogen balance and excessive loss of proteins were great factors in the disturbed body economy of the patient with pemphigus. For that reason, every effort was made to improve the altered albumin-globulin ratio. It was felt that such measures as transfusions of whole blood as well as plasma helped produce such improvement. In addition, patients were given protein hydrolysates intravenously and protein concentrate and high protein feedings by mouth. Perhaps this treatment is what helped convert the pemphigus vulgaris acutus of some patients to the chronic form. The methods used were reported in another communication.[6]

COMMENT AND SUMMARY

Results of laboratory studies on 19 patients with pemphigus vulgaris were divided into changes in the cellular elements and changes in chemical values. No effort was made to separate values for patients with the so-called acute pemphigus vulgaris from those for patients with the chronic type.

Some anemia was demonstrable in all the patients. The anemia became intense in some patients as the illness increased in severity and the patient became more toxic. Two patients revealed a hemolytic type of anemia with spherocytes demonstrable in the peripheral blood. The red blood cells of these two patients also exhibited abnormal fragility. The anemia was of a normocytic type and it disappeared as the toxemia became less severe.

The bone marrow examinations revealed only a hyperplastic marrow. Both the bone marrow and the peripheral blood exhibited an increase of eosinophiles. The sedimentation rate was increased in all the patients.

A battery of liver-function tests, which included studies of serum bilirubin, cephalin-cholesterol flocculation, sulfobromophthalein (bromsulphalein®) sodium retention, thymol turbidity, urinary Ehrlich reaction, urinary urobilinogen, and urinary coproporphyrin, was carried out for five patients. There were a few scattered abnormal results in some patients. None of the changes were of great significance, however.

The urinary coproporphyrin excretion was measured in seven patients and found to be increased up to seven times the normal amount.

The blood sodium and potassium levels were examined in all the patients at least once, and in many of them several times, during the course of the disease. There were no consistently abnormal changes which could be considered a reflection of the disease process.

6. Fisher, I.: Treatment of Pemphigus Vulgaris, Journal-Lancet **70**:18, 1950.

In all the patients examined, none of the levels for sodium was greatly depressed. Even in those with the relatively acute disease resulting in death, the blood sodium remained at a "safe" level.

The chloride levels were determined in a similar manner. The chloride levels did not seem to coincide with the patient's condition or course. There was a wide range in these levels.

Similar levels were determined in the spinal fluid and vesicle fluid. The levels of sodium, potassium, and chlorides in the vesicle fluid were almost identical with the blood levels determined for the same patient at the same time.

Values for the serum proteins and their various fractions were determined by a "salting-out" technique. The serum albumin decreased in all the patients, whereas the globulin level rose. The most evident rise was in the gamma globulin, and it compared with the rise reported in similar studies using the electrophoretic technique in the determination. The changes in serum proteins are tabulated for one patient as an example of the course observed in other patients as their illness varied from acute to chronic or vice versa. The serum protein levels became more abnormal, apparently as the disease progressed, and the albumin value increased again as the patient's condition improved. Serum protein levels in five patients with dermatitis herpetiformis are listed for comparison.

Dr. Elizabeth Frame, of the University of Minnesota, helped in the serum protein fractionation.

ABSTRACT OF DISCUSSION

DR. MAURICE J. COSTELLO, New York: The problem which Dr. Fisher has discussed is a difficult one. His study is another honest effort to determine a pattern, through laboratory studies, which may aid in the diagnosis and treatment of the inveterate cutaneous disease, pemphigus, whether of the vulgaris, foliaceus, or vegetans type.

It has been my experience that the degree of anemia in pemphigus parallels the severity of the illness, and this is especially true after relapses and exacerbations of the disease.

There is progressive elevation of the total leucocyte count in pemphigus, usually associated with clinical deterioration. In regard to the differential ratio, there is a shift to the left. By and large, most of these pemphigus patients were benefited by whole blood transfusions, which not only increased blood volume but replaced erythrocyte loss and possibly acted as a detoxifying agent.

In a small number of the patients suffering with pemphigus vulgaris whom my associates and I have observed, the eosinophile count was as high as 35% in the peripheral blood. A rather sudden elevation of the eosinophile count at times was associated with the onset of a generalized pruritic papulovesicular eruption, representing a short-lived exacerbation of the pemphigus eruption which had been in partial or complete remission. As a matter of fact, the eosinophile count has been as high, and often as persistent, as that observed in certain cases of dermatitis herpetiformis (Duhring's disease) of the bullous type and erythema multiforme pemphigoides. The eosinophile count in itself is of no value in differentiating the above diseases. A therapeutic trial with sulfapyridine is at times of great value in differentiating the so-called bullous type of dermatitis herpetiformis from pemphigus vulgaris. It is a routine procedure in our wards.

Results of liver-function tests in our experience have been within normal limits, and no light has been shed on the etiological possibilities of pemphigus vulgaris from abnormal liver function. A fact which has impressed me is that patients who have had severe, long-standing pemphigus vulgaris exhibit little demonstrable organic impairment when their disease is in full remission.

I do not believe that the rather significant increase in urinary coproporhyrin, as reported by Dr. Fisher, is of diagnostic or prognostic importance, as this substance may be increased in febrile, long-standing chronic diseases. Chronic passive congestion and fatty infiltration of the liver were observed in a number of necropsies performed at Bellevue Hospital on patients with this disease.

It is believed that there is a reduction in the blood volume, probably as high as 20%, in patients suffering with severe pemphigus vulgaris. This reduction is twofold. There is loss of plasma volume from exudation of fluid from abraded and denuded areas, and there is a loss in the total erythrocyte volume following nutritional loss, fever, superimposed infection, and toxemia. At this stage of the disease, there is considerable weight loss, 10 to 30 lb. (4.5 to 13.6 kg.).

It has been obvious that the maintenance of sufficient, if not optimal, blood volume is important in preventing what might be termed medical shock. I have seen patients suffering with extensive pemphigus vulgaris at a critical period suddenly display pallor, coldness of the extremities, rapid pulse, lowering of blood pressure, and shaking chills with fibrillary twitching of the muscles, followed by death in several hours.

The depletion presented by these pemphigus patients is somewhat analogous to the condition reported by Ling and Sprinz, who noted blood volume changes in soldiers with chronic wound infections and associated nutritional depletion (*Am. J. M. Sc.* **215**:555-567 [May] 1948).

Of necessity there must be a relation between the plasma proteins and the plasma volumes. It has always been our aim to restore the positive nitrogen balance by high protein diet and by the oral and parenteral administration of protein hydrolysates. Dr. William Mulvehill has found, in a study in the wards at Bellevue Hospital on a number of patients suffering with pemphigus vulgaris, that there was not only a reduction in the total amount of serum protein, but, in a number of cases, a reversal of the albumin-globulin ratio. This condition is probably explained by the loss of albumin through the urine or by its destruction in the effort of metabolism. Globulin is less affected in this manner, and it is more readily regenerated. This pronounced reduction of plasma protein may account for the edema seen in certain periods of pemphigus.

The clinicopathological reports from Bellevue Hospital on several hundred cases of pemphigus vulgaris fail to include the results of such studies as those undertaken by Dr. Fisher. However, studies on serum chlorides, sodium, potassium, blood urea nitrogen, total proteins, etc., were performed for the majority of patients with this disease. The results were not recorded because of our inability to arrive at any significant conclusions regarding their diagnostic importance.

Since Dr. Fisher has not drawn any conclusions from his laboratory data, he is probably of the same mind regarding them. The most disappointing fact in our series was that these chemical examinations of the blood were of no value in separating one bullous disease from another. It has been our experience that most bullous diseases which are severe and extensive will produce somewhat similar chemical changes in the blood. However, the interpretation of such chemical analyses was of considerable value in the selection of current supportive treatment.

As cortisone and corticotropin (ACTH) have brought relief in a number of diseases of obscure causation and at the same time helped to explain a common cause, there is still the hope that the complexity of the bullous diseases may yet be clarified through the continued study of the action of these hormones.

Dr. Isadore Fisher, Minneapolis: I certainly agree with Dr. Costello that most of the levels reported here are normal. The normal levels in the liver-function studies, those for chlorides and sodium as well as the others given, are no basis for definite conclusions. For that reason no conclusions are offered. One reason for compiling this study is that there has been an effort in the past to relate some of the levels to adrenal insufficiency. I could find no evidence of such insufficiency in my patients. I do not know what the abnormal coproporphyrin secretion means. It may simply be a reflection of the toxic state in the patient.

AUREOMYCIN AND ITS EFFECT IN EARLY SYPHILIS

One-Year Progress Report

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SEYMOUR WEINSTEIN, M.D.
AND
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CHICAGO

IN APRIL, 1950, in a progress report [1] based on a study of 67 patients with dark-field-positive syphilis, it was concluded that oral administration of 70 gm. of aureomycin over 11⅓ days causes a progressive decline in the serologic titer, rids syphilis lesions of surface spirochetes in an average of 39 hours, maintains high aureomycin blood levels, and shows cerebrospinal fluid aureomycin levels for 50% of the patients.

*Race, Sex, and Age of One Hundred Patients Having Dark-Field-Positive Secondary Syphilis Treated with Aureomycin**

Race and Sex	Total	Age, Yr.		
		Under 20	20-24	Over 24
Total	100†	10	45	45
Male	58	3	22	33
Female	42	7	23	12
White	18	..	6	12
Male	10	..	3	7
Female	8	..	3	5
Negro	82	10	39	33
Male	48	3	19	26
Female	34	7	20	7

* Treatment consisted of 68 doses of 70 gm. of aureomycin administered orally during 11⅓ days.
† Exclusive of one Indian woman 25 years old.

This paper was prepared under the direction of Herman N. Bundesen, M.D., President, Chicago Board of Health.

From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health, in cooperation with the United States Public Health Service.

Medical Director, Chicago Intensive Treatment Center; Research Associate, Kettering Foundation for Medical Research; Special Consultant, United States Public Health Service, Division of Venereal Disease (Dr. Rodriquez); Assistant Medical Director, Chicago Intensive Treatment Center (Dr. Weinstein); Venereal Disease Control Officer; Medical Officer in Charge, Chicago Intensive Treatment Center (Dr. Parkhurst).

1. Rodriquez, J.; Plotke, F.; Weinstein, S., and Harris, W. W.: Aureomycin and Its Effect in Early Syphilis: Progress Report, A. M. A. Arch. Dermat. & Syph. **63**:433-439 (April) 1951.

The present study is based on the results of observation for 12 to 15 months on 101 patients with dark-field-positive secondary syphilis. All patients were previously untreated for syphilis.

The distribution of patients by race, sex, and age is indicated in the table. The age range for the group was 17 to 69 years. The median age was 24 years. Eighty-two patients were Negro; 18 were white, and 1 was Indian. Fifty-eight were men, and 43 women. The patients were treated from March, 1949, through February, 1950.

TREATMENT SCHEDULE

Aureomycin in the following treatment schedule was administered by the oral route to each of the 101 patients: An initial priming dose of 2 gm. was given, and this dose was repeated four hours later; then 1 gm. was given every four hours, day and night, until a total of 70 gm. had been administered in 11⅓ days.

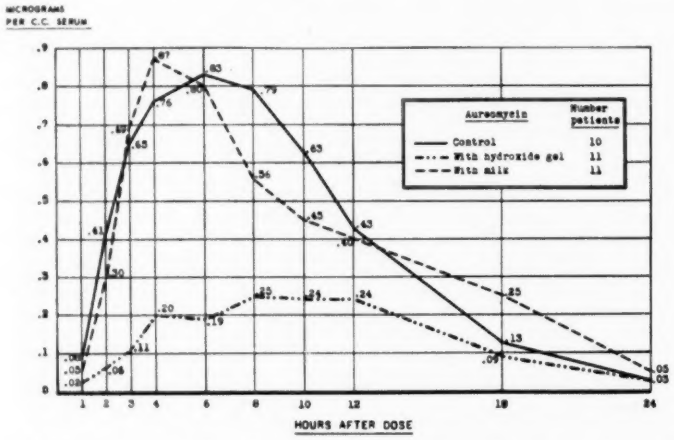

Fig. 1.—Average blood levels after oral administration of a single dose of 2 gm. of aureomycin, showing influence of ingestion of aluminum hydroxide gel and milk.

EFFECT ON LESIONS

Open lesions of syphilis healed completely with aureomycin therapy in every instance, though the time interval seemed to be somewhat more prolonged than that with treatment by the trivalent arsenical compounds or aqueous penicillin. Secondary syphilis lesions involuted completely.

EFFECT OF ALUMINUM HYDROXIDE GEL AND MILK ON AUREOMYCIN BLOOD LEVELS

In view of the frequent use of aluminum hydroxide gel or milk to alleviate the symptoms of nausea and/or emesis in patients on this schedule of aureomycin administration, a control study was initiated to observe the effects of these two agents on the blood levels after oral administration of a single 2-gm. dose of aureomycin.

As shown in Figure 1, assayable levels were revealed for an average duration of 18.2 hours, with a peak concentration of 0.83 γ per cubic centimeter of serum in the sixth hour, for 10 patients in the control group; for an average duration of

20.2 hours, with a peak concentration of 0.87 γ in the fourth hour, for 11 patients in the milk group, and for an average duration of 11.5 hours, with a peak concentration of 0.25 γ in the eighth hour, for the 11 patients in the aluminum hydroxide gel group.

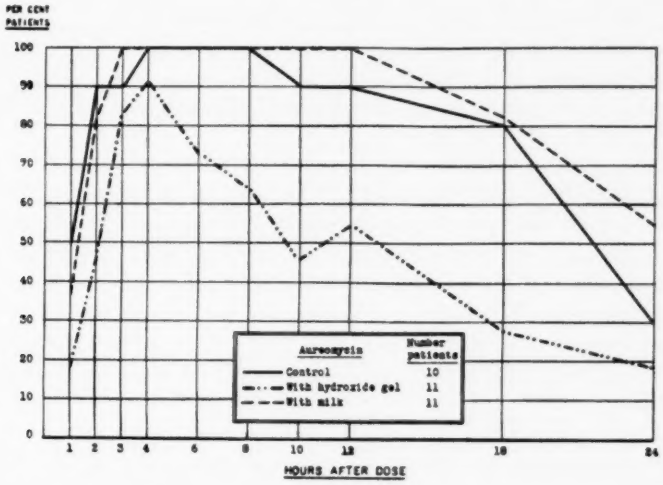

Fig. 2.—Percentage of patients showing aureomycin blood levels after a single oral dose of 2 gm.

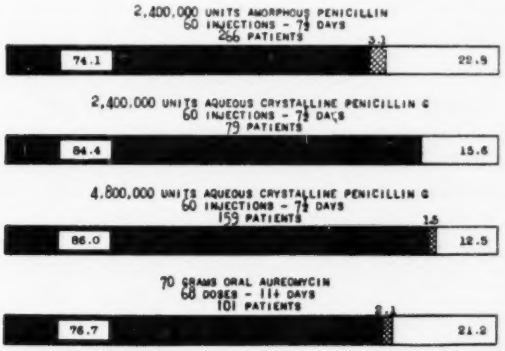

Fig. 3.—Cumulative results of treatment of dark-field-positive secondary syphilis in 12 to 15 months' observation. Gray areas indicate number of patients in whom treatment was successful; cross hatched areas, number of patients with reinfection; white areas, number of patients in whom treatment failed.

These figures demonstrate a 43.1% decrease in the average duration and a 71.3% decrease in the peak concentration for the aluminum hydroxide gel group as compared with the milk group. Figure 2 similarly indicates a much lower percentage of patients in the aluminum hydroxide gel group showing assayable aureomycin levels.

TREATMENT RESULTS

Satisfactory follow-up observations were made on 90% of the total 101 patients in this study.

The cumulative percentages of treatment results [2] at the end of the 12 to 15 months' observation period for the 101 patients treated are shown in Figure 3: 76.7% cases were classified as successes, comprising 66.2% seronegative and 10.5% with 3 Kahn units or less in the serum; 2.1% were classified as reinfections, and 21.2% were classified as failures, comprising 7.0% clinically normal but with 4 Kahn units or more in the serum and 14.2% declared clinical or serologic failures.

TIME TO REACH SERONEGATIVITY

Of the total 101 patients, 70, or 69.3%, were known to be seronegative some time within the 15 months' observation period. Twenty-five patients, or 24.8% of the 101 patients, became seronegative within three months, and 58, or 57.4%, within six months. Of the 70 patients who reached seronegativity, 9, or 12.8%, were later classified as failures: 4 as clinical failures, 4 as serologic failures, and 1 showing reinfection.

The seronegativity rate was 66.2% at the end of the 12 to 15 months' observation period.

CEREBROSPINAL FLUID EXAMINATIONS

Cerebrospinal fluid examinations were performed for each patient in the study; 87.1% revealed normal [3] pretreatment findings, and 12.9%, abnormal results. The neurorecurrence rate for 63 patients with post-treatment cerebrospinal fluid examinations was 1.6%. Nine patients with abnormal pretreatment findings were reexamined some time during the 15 months. Six became normal; one improved, and two showed no improvement.

PREGNANCIES

Seven patients became pregnant after treatment and were not re-treated. Of these pregnancies, five terminated in live births and two in fetal deaths. Of the five live infants, all were clinically, serologically, and roentgenologically normal. The minimum observation period in this group was 3 months and the maximum 14 months. Of the two fetal deaths, one was a criminal abortion and the other a spontaneous abortion of nonsyphilitic origin.

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2. The percentages used for the figures on successes and failures were obtained by assuming that patients lost from observation would have shown the same ratio of results of treatment as those observed. The ratio of the number of patients observed in each period to the number observed in the preceding period was applied to the cumulative failure figure. Patients with positive significant titers (4 Kahn units or more) after 12 to 15 months' observation have been grouped with failures. Those who were seronegative or who maintained nonsignificant titers (3 Kahn units or less) were, for the present, considered successes. This method of evaluation is considered rigid, and, as a consequence, the failure rate tends to be relatively higher than in similar studies utilizing less rigorous criteria.

3. The criteria for normal cerebrospinal fluid were as follows: a negative Kahn reaction; a cell count of seven lymphocytes or fewer; a total protein level of 45 mg. per 100 cc. or less, and a negative reaction to the colloidal gold test.

REACTIONS

Febrile Herxheimer reactions occurred in 16, or 15.8%, of the 101 patients treated. No cutaneous Herxheimer reactions were noted. Secondary fever was recorded for three patients. Nausea was reported for 72.3% of the patients and emesis for 56.4%. Those patients exhibiting gastrointestinal disturbances did so after the 12th hour; the incidence was highest on the third day and tapered off thereafter, even though the dose schedule remained unchanged. Milk, aluminum hydroxide gel, glucose, and fruit juices all helped to minimize gastrointestinal reactions, but the definite decrease in nausea and emesis among the latter half of the treated patients was most likely due to the improvement in purification of the aureomycin by the manufacturer.

Results of laboratory examinations of the urine and the blood, the icterus index, and determinations of the nonprotein nitrogen levels before, during, and after treatment were essentially normal.

COMMENT

Evaluation of the results on treatment of the 101 patients in the aureomycin study is being made by comparisons with the cumulative percentages of treatment results for a 12 to 15 months' observation period on patients with dark-field-positive secondary syphilis in three other studies analyzed at this center. In these studies 2,400,000 units of aqueous amorphous penicillin,[4] 2,400,000 units of aqueous penicillin G,[5] and 4,800,000 units of aqueous penicillin G [6] were administered in 60 intramuscular injections over seven and one-half days.

As shown in Figure 3, the seronegativity rate is higher for the 4,800,000-unit penicillin schedule than for the aureomycin schedule, although statistically there is no significant difference.

When satisfactory results are used as the yardstick of evaluation, we find no significant difference between those obtained with the 4,800,000-unit penicillin schedule (86%) and those obtained with the aureomycin schedule (76.7%).

Applying cumulative failure rates as the criterion for comparison, we again find no significant difference between those with the 4,800,000-unit penicillin schedule (12.5%) and those with the aureomycin schedule (21.2%).

Similarly, on comparing the 2,400,000-unit aqueous penicillin schedules, using crystalline penicillin G and amorphous penicillin, with the aureomycin schedule, we find no significant differences in seronegativity rates, satisfactory results, or failure rates.

It is now definite that aureomycin has a therapeutic effect in early syphilis comparable with that of the penicillin schedules herein described.

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4. Bundesen, H. N.; Plotke, F.; Schwemlein, G. X., and Rodriquez, J.: Penicillin in the Treatment of Early Syphilis: 639 Patients Treated with 2,400,000 Units of Sodium Penicillin in 7½ Days, J. Ven. Dis. Inform. **30**:321-324 (Nov.) 1949.

5. Schwemlein, G. X.; Plotke, F., and Rodriquez, J.: Crystalline Penicillin G Versus Amorphous Penicillin: Treatment of Early Syphilis, J. Ven. Dis. Inform. **31**:155-159 (June) 1950.

6. Plotke, F.; Rodriquez, J., and Schwemlein, G. X.: The Total Dosage Factor in the Use of Crystalline Penicillin G: The Treatment of Early Syphilis, Am. J. Syph. **35**:246 (May) 1951.

Similar favorable results with aureomycin in the treatment of early and late cutaneous manifestations and neurosyphilis were reported by O'Leary, Kierland, and associates,[7] and by other investigators.[8]

SUMMARY AND CONCLUSIONS

One hundred one patients having secondary syphilis with dark-field-positive lesions were given 70 gm. of aureomycin orally in 11⅓ days.

The cumulative percentages of treatment results by the end of the 12 to 15 months' observation period for the 101 patients were 76.7% successes, 2.1% reinfections, and 21.2% failures.

Aureomycin rid syphilis lesions of surface spirochetes in an average of 39 hours.

No serious reactions were noted. The incidence of gastrointestinal disturbances after the introduction of the improved aureomycin dropped approximately 50%.

High and sustained blood levels of aureomycin were easily maintained by use of the oral route.

Ingestion of aluminum hydroxide gel caused a 43.1% decrease in the average duration of assayable aureomycin levels and a 71.3% decrease in the peak concentration, as compared with results on ingestion of milk.

Cerebrospinal fluid aureomycin levels were not detected after a single 2-gm. oral dose, but were present for 50% of the patients during the multiple-oral-dose schedule.

A one-year evaluation of this study makes it possible to state that a new agent, aureomycin, is an additional weapon in the treatment of syphilis. Continued studies are necessary to determine its long-range effectiveness.

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MOUSE RINGWORM

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ANIMALS are carriers of many diseases and parasites that may be transmitted to man, among which are cutaneous fungous infections. Mice are susceptible to infection by dermatophytes, and man, in whom dermatophytoses occur frequently, is occasionally infected by these fungi through exposure to diseased mice or to an intermediate animal or object. Achorion quinckeanum infections are the commonest mycotic infections of mice, and, though rarely occurring in the United States, they are not uncommon in Europe and Australia. Trichophyton mentagrophytes infections of mice are apparently rare, for there is very little mention of them in the literature, and I am aware of no reports of them from the United States.

ACHORION QUINCKEANUM INFECTIONS

Favus is a dermatophytosis characterized by the formation of crusts known as scutula and caused by several varieties of Achorion. Among animals [1] it occurs most commonly in mice and rats and less frequently in cats, dogs, and rabbits. Man is susceptible to infection by the organisms causing animal favus, as well as by Achorion schoenleini.

Achorion quinckeanum is the species which causes mouse favus. This disease may occur among mice in epizootic proportions and may be highly fatal to them. It produces severe crusted lesions in mice, especially about the head and eyes, destroying the cornea and resulting in blindness. Death ensues from starvation. The manifestations of Achorion quinckeanum infections in man are circinate, scaling, erythematous lesions known as favus herpeticus or herpes circinatus. Faviform crusts in man due to this organism are much rarer than the ringworm-like lesions, and some authors deny that they occur.

Favus in the mouse was first recorded in England in 1850 by Bennett,[2] who observed a common house mouse in which the vegetations of favus detected were the same as those in man. The species causing mouse favus was named Achorion quinckeanum after Quincke,[2] who studied the fungi of favus, differentiated the organism of mouse favus from that of the human type, and concluded that favus of the smooth skin in man is usually of murine origin.

Sabouraud [2] in his treatise on fungi concluded that there are distinct types of faviform fungi to be found in animals, but that proved instances of transmission

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From the Department of Dermatology and Syphilology of Indianapolis General Hospital.

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to man are rare. Bloch [2] disagreed with Sabouraud, stating that in his experience the mouse favus fungus producing the body lesions in man was commoner than the typical faviform head fungus of man. He recognized three fungi capable of producing favus in man: Achorion schoenleini, Achorion quinckeanum, and Achorion gypseum. Later, he described Achorion violaceum, which he cultivated from four human subjects with dermatophytosis. Two of the patients lived in a house in which mice having faviform lesions were caught, the same fungus being cultivated from mice and man.

In Australia [3] there have been plagues of mouse favus among wild mice. A number of workers who handled stored wheat that had been contaminated by these mice exhibited faviform lesions of the glabrous skin. Achorion quinckeanum was isolated from both mice and men.

A few instances of mice infected with dermatophytes have been noted in the United States. The first American case of human favus contracted from animals was reported by Draper [2] in New York. He detected favus in a trapped mouse, and the infection evidently had been transmitted from this mouse or other infected mice to a cat, and from this animal to two children. Sherwell [2] described a number of cases in which human beings contracted favus from a dog with favus that apparently had been infected by mice and rats. Many rodents infected with favus were observed.

Buchanan [4] in 1919 reviewed the literature on mouse favus and concluded that a distinct disease, mouse favus, does exist commonly in Europe and Australia and probably more rarely in the United States. He stated that there was abundant evidence of the transmissibility of the disease from mouse to man, producing the favus herpeticus of the glabrous skin.

The formation of crusts [5] clinically and the resemblance of the cultures to those of Achorion schoenleini led early investigators to place Achorion quinckeanum in the Achorion genus. Later authors claimed, however, that this species was more closely related to the Trichophyton and Microsporum genera than to Achorion schoenleini. Moore [6] stated that Trichophyton mentagrophytes and Achorion quinckeanum are related but not identical. Other mycologists have eliminated the genus Achorion and distributed its species to other genera. According to Conant,[7] Achorion quinckeanum is synonymous with Trichophyton mentagrophytes. Skinner, Emmons, and Tsuchiya,[8] placed Achorion quinckeanum in the Trichophyton genus. Plaut and Grutz [9] stated that all the members of this group are very closely related to one another and are further linked by a number of transitional forms, so that hard and fast lines cannot be drawn between them.

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7. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944.

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9. Plaut and Grutz, cited by Hutyra and others.[1]

TRICHOPHYTON MENTAGROPHYTES INFECTIONS

The occurrence of Trichophyton infections in mice with transmission of the organism to man has been described by Parish and Craddock,[10] who published an account of an epizootic in England in which 50% of a breeding stock of 2,500 mice were infected with Trichophyton mentagrophytes asteroides. Four laboratory assistants were infected from the mice; in these persons the infection produced papulovesicular rings on the forearms and an eczematoid eruption on the hands. DuBois [11] and Catanei [12] also described natural infections of mice with Trichophyton mentagrophytes, but made no mention of transmission of the disease to man.

REPORT OF A CASE

D. L., a white woman, 24 years of age, was first observed by me on Jan. 31, 1951. She complained of an eruption on both hands that itched moderately and was of two months' duration. She was a laboratory technician and handled white mice in her work. She stated that many of the mice in the laboratory had areas of hair loss.

Examination of the patient disclosed groups of superficial vesicles on the hands and fingers. Tissue from these vesicles in a potassium hydroxide preparation showed numerous mycelia on direct microscopic examination. Cultivation on Sabouraud's dextrose agar resulted in the growth of a white, granular fungus colony which was identified as Trichophyton mentagrophytes.[13] Treatment with potassium permanganate compresses and a salicylic acid ointment resulted in a cure within three weeks.

EPIZOOTIC OF RINGWORM IN WHITE MICE

Numerous white mice in the laboratory where the patient was employed were affected by a skin disease manifested by loss of hair (Fig. 1) and increased scaling. The bald areas were irregular in shape and size, with indistinct margins. These were predominantly on the dorsum of the head and back, the abdomen rarely being affected. There were some broken hairs, and the remaining hair was brittle, lusterless, and unhealthy in appearance. The only visible inflammation of the skin was increased scaling. There were no pustules or crusts, and the hair did not fluoresce under the Wood light.

A small, spored ectothrix was observed on microscopic examination of mouse hairs in a potassium hydroxide preparation. A few mycelia were found with difficulty in a potassium hydroxide preparation of the skin. Trichophyton mentagrophytes granulatum (Fig. 2) was isolated from 10 mice with bald spots by inoculation of hair on Sabouraud's dextrose agar.

No accurate estimate of the total number of infected mice in the laboratory could be made. The firm by which the patient is employed uses approximately 900 new mice daily in its laboratories. These are furnished by several commercial breeding laboratories; this makes the mouse population a constantly changing one and renders epidemiologic surveys of little value.

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11. DuBois: Trychophytie spontanée de la souris grise avec quelques considérations sur l'évolution naturelle de l'infection, Ann. dermat. et syph. **10**:1359 (Dec.) 1929.

12. Catanei, A. L.: Natural Tinea of White Mice in Algiers, Arch. Inst. Pasteur Algérie **20**:305 (Dec.) 1942.

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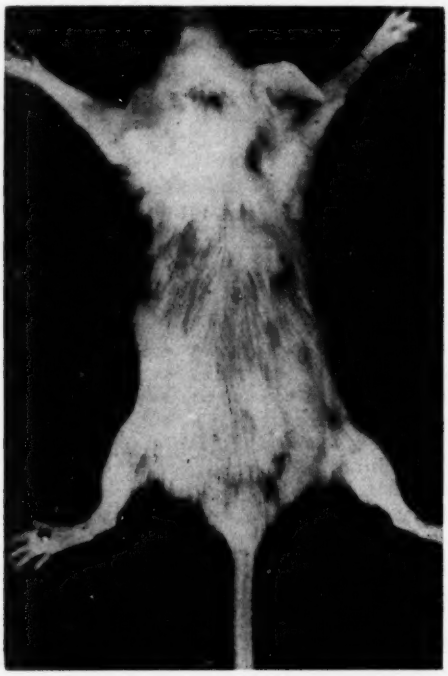

Fig. 1.—Ringworm-infected white mouse showing irregular areas of alopecia.

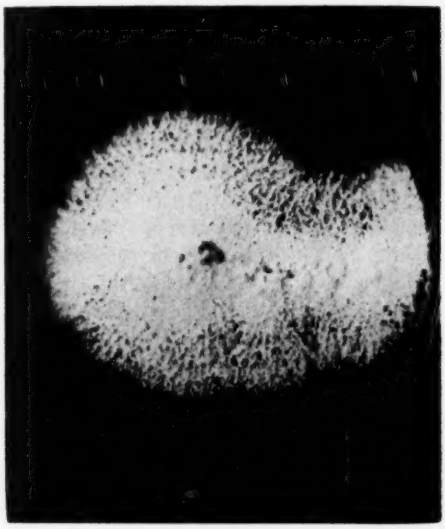

Fig. 2.—Culture of Trichophyton mentagrophytes isolated from a white mouse.

The source of the diseased mice was discovered to be a breeding laboratory. All of 12 young, apparently healthy mice from this laboratory, shipped directly to the Mycology Laboratory of the Dermatology Department of Indianapolis General Hospital, showed Trichophyton mentagrophytes granulatum on cultures. The owner of the commercial laboratory stated that there had been no ringworm infections in his employees. Permission to study the mice in his laboratory was not granted.

Letters were sent to eight other mouse-breeding laboratories, inquiring if any employee had ringworm of the exposed parts. All answered, one in the affirmative. This owner stated that three of seven employees had ringworm of the forearms and hands. He also described bald spots in the young mice which disappeared as they matured; this fact is consistent with the observation that ringworm thrives in young animals. In 19 mice from this laboratory, cultures failed to grow pathogenic fungi.

Six additional mice infected with Trichophyton mentagrophytes were discovered in the animal laboratory of the Indiana University Medical School. These mice were from a different breeding laboratory. They were also infested with lice. The mousery which furnished the ringworm-infested mice mentioned earlier also supplied some of the mice present in this laboratory. Since there could be no transmission of the disease by direct physical contact, the lice were thought to be a possible means of transmission from animal to animal.

Trichophyton mentagrophytes was isolated from a total of 28 white mice. These were discovered in one commercial breeding laboratory for mice and in two scientific laboratories which obtained some of their mice from this commercial laboratory. These results indicate an epizootic of ringworm in the commercial breeding laboratory.

SUMMARY AND CONCLUSIONS

The literature on cutaneous fungous infections of mice with transmission of the disease to man is reviewed. An epizootic of Trichophyton mentagrophytes infection of white mice, with transmission of the disease to a laboratory worker, is described. From the scarcity of reports on them, Trichophyton mentagrophytes infections of mice appear to be rare, but the disease may be unnoticed and more widespread than suspected.

CLINICAL EXPERIENCE WITH "POLYCIN," A POLYMYXIN-BACITRACIN OINTMENT

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RECENT years have witnessed the advent of a number of new agents for local therapy in pyogenic infections of the skin. Certain of these, however, are not without disadvantages. Topical use of the sulfonamides and penicillin, while very effective, has resulted in sensitization in at least 5 and 10% of the cases, respectively,[1] with indications that reactions to penicillin are increasing both in frequency and in severity. The use of nitrofurazone (furacin®) has likewise resulted in a significant degree of sensitization, reactions occurring in about 5% of the cases.[2] Good results have been reported[3] for dihydrostreptomycin in topical therapy, with sensitization manifested in 3.7% of patients treated. Prolonged use of this drug was not recommended, however, because of the rapid development of drug-fastness. The incidences of reactions obtained with the sulfonamides, penicillin, and dihydrostreptomycin thus become of importance, especially since these drugs are intended mainly for systemic application.

Sulzberger[4] recently claimed favorable results with aureomycin ointment, but found it to have certain drawbacks. Although in many cases there was rapid improvement with this therapy, recurrences were experienced in a number of instances while treatment was still being given. Lack of continued effectiveness was believed to be due to drug-fastness, aureomycin thus paralleling dihydrostreptomycin in this respect. On the other hand, aureomycin was found to possess a low index of sensitization. Neomycin has also been reported to be effective in treatment of various pyogenic skin infections.[5] However, development of bacterial resistance

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"Polycin" is a trade name of Pitman-Moore Company, Division of Allied Laboratories, Inc., Indianapolis 6.

Chairman, Department of Dermatology and Syphilology, Indiana University School of Medicine (Dr. Gastineau).

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5. Kile, R. L.; Welsh, A. L., and McAfee, G. D.: Topical Use of Neomycin, Arch. Dermat. & Syph. **62**:911 (Dec.) 1950.

to this drug, especially by species of Proteus and Pseudomonas, has likewise been demonstrated.[6]

Perhaps the least allergenic of local agents currently used is bacitracin, with a reported sensitization rate of less than 0.5%.[7] Although extremely effective in local treatment of pyogenic infections,[8] bacitracin has been found to exert its antibacterial action in vitro chiefly against Gram-positive bacteria.[9] With the exception of the Gonococcus (Neisseria gonorrhoeae) and Meningococcus (Neisseria meningitidis), Gram-negative organisms are resistant. Fungi are also resistant to the antibiotic, while spirochetes have shown marked susceptibility.[10]

Considerable attention has recently been given to the polymyxins, a group of closely related antibiotics effective mainly against Gram-negative bacteria [11] and certain pathogenic fungi.[12] Isolated from various strains of Bacillus polymyxa, the polymyxins, five of which have been identified and designated as varieties A, B, C, D, and E, are basic polypeptides differing from one another in amino acid composition. A salient feature of these antibiotics is that bacterial resistance is produced only with great difficulty.[13] In effective concentrations the polymyxins are bactericidal in action and do not appear to be appreciably antagonized by blood or serum. They are stable at room temperature in the dry state, and solutions have been kept refrigerated for at least two weeks without loss of potency. The successful use of polymyxin B has been reported in influenzal meningitis,[14] shigellosis,[15] and urinary tract infections due to Escherichia coli, Aerobacter aerogenes, and Pseudomonas aeruginosa.[16] Of special interest is the fact that the polymyxins have been

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found to be the most effective of currently available antibiotics against Ps. aeruginosa, the etiological significance of which is becoming more recognized in a number of diseases, particularly otitis externa and media, and suppurating wounds and burns. A study of the topical use of polymyxin B has been reported [17] in which granulating wounds infected with Ps. aeruginosa were sterilized after application of the antibiotic in saline solution or polyethylene glycol (carbowax®) base. A significant finding was the fact that none of the usual reactions indicative of sensitization developed in any of the patients.

In a search for a relatively nonallergenic preparation for topical use and one which would be active against a wide variety of micro-organisms, the above facts suggested the clinical use of a combination of polymyxin B sulfate and bacitracin.

Because of differences in diffusibility and stability of polymyxin and bacitracin, a number of ointment bases were studied before one was found which afforded maximum release of the antibiotics and in which both types of agents remained stable over a sufficient length of time. The base [18] found most suitable consisted of (1) liquid petrolatum, (2) white petrolatum, (3) a polyhydric alcohol fatty acid ester ("glyco wax S932), (4) polyethylene glycol 400 di-stearate, and (5) polyethylene glycol 400 di-laurate. Polymyxin B sulfate was incorporated at a concentration of 8,000 units per gram of base, and bacitracin, at that of 400 units per gram.

EXPERIMENTAL STUDY

Before attempting clinical evaluation of the polymyxin-bacitracin ointment, the relative effectiveness of each antibiotic singly and in combination was first determined in artificially infected wounds in rabbits.

The dorsal area of rabbits was denuded of hair, and with the animals under light anesthesia sections of skin were excised so that circular wounds approximately 1.5 cm. in diameter resulted. Six wounds adequately spaced were thus produced on each animal. Twenty-four-hour blood broth cultures of the following organisms were used to infect the wounds: Proteus vulgaris, Ps. aeruginosa, a Group A beta hemolytic Streptococcus (C203), and a hemolytic strain of Staphylococcus aureus. In order to test the specificity of each antibiotic, wounds were at first infected with single cultures of the various organisms. In subsequent experiments, a mixed culture of Ps. aeruginosa and Staph. aureus was used. Infection was accomplished by rubbing 0.1 cc. of undiluted culture into the wound with a sterile swab. Two of the wounds on each rabbit served as controls on the infection, while the remaining four were treated. In testing the single cultures, only one species was used per animal.

Treatment was instituted immediately after wound infection and was continued once daily for three consecutive days. A fixed quantity of ointment was applied in each case and covered with a sterile dressing. Cloth jackets were secured around the rabbits to prevent removal of the bandages. Single ointments used in treatment contained 8,000 units of polymyxin B sulfate and 400 units of bacitracin, respectively, per gram of base. A mixture of the two antibiotics in the above concentrations was employed for combined therapy. The antibacterial effects of polymyxin and bacitracin were determined by daily subculture of material from the wounds onto suitable media. Blood agar was used for the staphylococcal and streptococcal infections, while desoxycholate agar served for the Proteus and Pseudomonas infections. All plates were incubated at 37 C. for 48 hours, and the resulting growth was noted.

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EXPERIMENTAL RESULTS

Data obtained from these experiments indicated that polymyxin alone was markedly effective in decreasing the numbers of organisms in wounds infected with either P. vulgaris or Ps. aeruginosa. As would be expected, polymyxin had no apparent effect on the Staphylococcus or Streptococcus. Treatment of the mixed infections with bacitracin alone usually resulted in complete eradication of the Staphylococcus organisms after one application, although the numbers of Ps. aeruginosa organisms remained unaffected throughout treatment. Application of combined antibiotic ointment to either single or mixed infections resulted in most instances in complete sterilization of wounds. In some cases, this occurred after only one treatment.

CLINICAL STUDY

The therapeutic response to polymyxin B sulfate and bacitracin ointment ("polycin") was observed in 147 patients with dermatoses. Seventy-two were treated for primary superficial infections and 75 for secondary bacterial infections accompanying various underlying conditions. All

Results of "Polycin" Therapy in Primary and Secondary Skin Infections

Diagnosis	No. of Patients						Average No. of Days Required for Cure
	Treated	Cured	Improved	With Treatment Failure	With Reaction to Medication	With Previous Antibiotic Treatment	
Impetigo contagiosa	34	33	..	1	0	7	6.2
Sycosis barbae	12	8	4	0	1	3	10.5
Abscess	6	6	..	0	0	1	10.2
Folliculitis	6	5	1	0	0	3	12.4
Chronic infected granulomatous ulcer	5	5	..	0	0	2	10.6
Infectious eczematoid dermatitis	5	4	1	0	0	0	17.0
Miscellaneous	4	3	1	0	0	1	7.0
Secondary infection in various dermatoses	75	71	2	2	0	12	11.6
Total	147	135	9	3	1	29	

patients in the present series were seen in private practice. Results of treatment are summarized in the accompanying table. Of the 72 patients treated for primary infections, complete cures were obtained in 64 patients, 7 showed definite improvement, and only 1, who had an impetigo involving the bearded area of the face, failed to respond to "polycin." One patient with sycosis barbae had what appeared to be a reaction on the 15th day of treatment, at which time medication was discontinued despite improvement.

It will be observed that "polycin" treatment of 75 patients having various dermatoses with secondary bacterial infections resulted in complete elimination of the infection in 71. Improvement but not complete cure was attained in two patients. One patient with infected eczema and a chronic vesiculopustular dermatitis was not benefited. It was of interest that 29 of the patients treated with "polycin" had failed to respond to previous antibiotic therapy. Seventeen had received penicillin either locally or parenterally; one of these, a patient with impetigo, was treated with both penicillin and bacitracin topically. Bacitracin ointment alone was used for 10 patients; 1 patient with folliculitis was treated locally with both bacitracin and aureomycin, and for 1 patient with impetigo tyrothricin ointment was used. All but 1 of the 29 patients receiving previous antibiotic therapy were cured of bacterial infection after the use of "polycin."

Bacteriological studies were made for 31 of the patients treated with "polycin." Staphylococci were isolated from every lesion examined. Twenty-nine of the patients harbored the hemolytic variety, pure cultures of which were obtained from 14, while nonhemolytic staphylococci were obtained from the 2 remaining patients, from 1 in pure culture. In the 16 patients whose lesions

showed mixed flora, the staphylococci were found associated with the usual types of bacteria commonly isolated from superficial skin infections. Gram-negative organisms were cultured from lesions of nine patients presenting mixed infections. A. aerogenes appeared in cultures from four patients and Proteus mirabilis in those from two, with 1 of these patients, who had an infected eczema, harboring both of the species. Esch. coli was isolated from one patient, Escherichia freundii from one patient, and Alcaligenes faecalis from another. A Gram-negative rod found in the lesions of a patient with infected contact dermatitis was not identified. Complete cures resulted in all but one of the patients from whose lesions Gram-negative organisms were isolated. The one patient with sycosis barbae was showing improvement when seen after 11 days of treatment, but he failed to return. The response of these patients to "polycin" is illustrated below.

REPORT OF CASES

Case 1.—I. M., a 26-year-old man, had ringworm with secondary bacterial infection which started on the upper lip and extended over much of the face. Treatment with wet packs and penicillin was ineffective. Cultural study showed the presence of Trichophyton mentagrophytes, a hemolytic Staphylococcus, a Gram-positive anaerobic spore-forming rod, and A. aerogenes. Application of "polycin" three times daily for 14 days resulted in complete clearing of the infection.

Case 2.—H. R., a 25-year-old man, presented an infected dermatitis of the right hand which had persisted for two years. Various local treatments throughout this period had failed. Cultures revealed a nonhemolytic Staphylococcus, a hemolytic Streptococcus, a Gram-positive aerobic nonsporing rod, and Esch. freundii. "Polycin" applied three times daily cured the infection within 14 days, with some residual dermatitis.

Case 3.—B. P., a 15-year-old girl, presented a fungal infection of both hands with secondary invasion. The condition had been active for about two months, but previous attacks had occurred during the past 10 years. Local treatment with a number of different preparations had consistently failed. Previous treatment had included penicillin given parenterally as well. The presence of a hemolytic Staphylococcus, an anaerobic Streptococcus, and A. aerogenes was demonstrated. "Polycin" applied three to four times daily for one month cleared the infection entirely.

Case 4.—S. S., a 31-year-old man, had an ulceration of the anterior tibial surface of the left leg of eight months' duration. Previous treatment with bacitracin ointment, hydrogen peroxide, sulfanilamide powder, and aluminum acetate (Burow's) solution proved unsuccessful. A culture revealed a hemolytic Staphylococcus, a Gram-positive Diplococcus, a Gram-positive nonsporing rod, and P. mirabilis. One week after "polycin" treatment was initiated, the lesion was dry and healing, with practically complete clearing of infection at 14 days.

Case 5.—C. C., a 27-year-old man, presented folliculitis decalvans of seven years' duration. Local application of a variety of preparations had failed to benefit. Penicillin administered parenterally was also without effect. The bacterial flora consisted of a hemolytic Staphylococcus, a Gram-positive Diplococcus, and Esch. coli. Application of "polycin" three times daily for 14 days resulted in a complete cure.

COMMENT

Results of the present study indicate that the superiority of bacitracin in local treatment may be greatly enhanced when the antibiotic is used in combination with polymyxin B. The base in which the antibiotics were incorporated has been found well suited for the stability of the antibiotics and for their release from the base. As determined quantitatively by the seeded-agar assay method, diffusion was much more rapid from the new base than from the conventional grease-type bases.[18]

In addition to its marked efficacy in treatment of infections of mixed bacterial origin, "polycin" appeared to possess an index of sensitization no greater than that demonstrated for bacitracin alone, and, since sensitivity to bacitracin is very rare, there would be little danger from frequent and prolonged use.

It is noteworthy that while "polycin" proved effective in clearing the bacterial elements in patients with various secondarily infected dermatoses, in no instance did it excite or aggravate the underlying skin conditions, which included such diseases as dermatophytosis, contact dermatitis, eczema, psoriasis, and neurodermatitis. In several cases of dermatophytoses, there was some indication that the fungal infection had been benefited also, which may signify that the continued activity of such lesions is often due to bacterial infection. Further study of the relative merits of "polycin" in secondarily infected dermatophytoses seems warranted.

SUMMARY AND CONCLUSIONS

One hundred forty-seven patients with superficial infections of the skin were treated with "polycin," an ointment containing a mixture of polymyxin B sulfate and bacitracin.

Only three patients in the present series failed to respond to treatment.

Bacteriological studies showed that "polycin" was especially effective in controlling lesions harboring both Gram-positive and Gram-negative organisms.

The low rate of sensitization so far observed makes the ointment an ideal preparation for topical use.

Although 75 patients were treated for bacterial infections superimposed on other skin diseases, in no instance did "polycin" excite or aggravate the primary condition.

ASSOCIATION OF CARCINOMA AND MYCOSIS FUNGOIDES

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THE ASSOCIATION of carcinoma and lymphoblastoma of any type is not common; the simultaneous occurrence of carcinoma and mycosis fungoides is especially rare. We have recently observed two cases in which this association occurred.

REPORT OF CASES

CASE 1.—G. B., a 50-year-old white woman, first noted a skin eruption at the age of 37 years. When first seen at the Dermatology Clinic of Northwestern University Medical School, at the age of 42 years, she presented on both breasts and buttocks oval and round maculopapular squamous lesions which were discrete and sharply marginated. At that time the clinical diagnosis was parapsoriasis en plaques. She then went to Florida, where the eruption improved after exposure to sunlight, but it never completely disappeared.

The past history revealed late latent syphilis for which she was treated from September, 1937, to January, 1940, with 13 injections of neoarsphenamine, 35 injections of oxophenarsine hydrochloride (mapharsen®), and 63 injections of a bismuth preparation. In 1948, while in Florida, she was given 600,000 units of penicillin daily for 10 days. The spinal fluid examination on two occasions was reported as showing nothing abnormal, and the blood serologic reaction (Kahn) was reported as "doubtful" at the last examination.

In November, 1948, when she was 48 years old, she was treated for carcinoma of the cervix. Therapy consisted of 6,000 r of roentgen rays through four portals. The factors used were 200 kv., 20 ma., at 50 cm. distance, 1 mm. Cu and 1 mm. Al filters, and half-value layer 1.34 mm. Cu.

She was again seen in August, 1950, with lesions on the trunk, axilla, and leg. On the back and trunk there were scattered, oval, slightly raised, mildly erythematous, soft, finely scaling lesions, 2 to 4 cm. in their longest dimensions. In the left axilla there were two slightly elevated, well-demarcated, erythematous, soft lesions, measuring 3 by 5 cm. and 1.5 by 2.5 cm., which showed slight scaling. On the medial aspect of the left leg and ankle there was an irregularly shaped, palm-sized area with slightly atrophic reticulated depigmentation and eczematous distal margins containing crusted erosions. Above the left malleolus was an oval, 4- by 6-cm., erythematous, slightly infiltrated lesion with loosely attached thin scales over the entire surface. The histological diagnosis for this lesion and for one of the lesions on the back was mycosis fungoides. She was then presented at a meeting of the Chicago Dermatological Society, where the diagnosis of mycosis fungoides was accepted.

Physical examination disclosed no lymphadenopathy, and the spleen and liver were not palpable. The cervical lesion had healed completely. The blood pressure was 175/108. The hemogram was normal.

Treatment of the skin lesions has consisted of five exposures, 88 r each, of superficial roentgen rays to each of the involved areas.

From the Department of Dermatology, Northwestern University Medical School, Herbert Rattner, M.D., Chairman.

CASE 2.—R. B. C., a 58-year-old white man, stated that he had been well until 15 months previously, when his "bladder stopped up." He was treated with prostatic massage and sulfanilamide tablets. Two months later he noted flat red spots around the knees which rapidly spread to involve other areas and became generalized within two months. Some of these lesions were thickened and scaling, and others formed nodules. The eruption had been nonpruritic. A physician then told him that he had "change of life" and treated him with hormones. For the past five months he had noted weakness, malaise, hoarseness, and difficulty in breathing. For the past five weeks he had pain in the joints of the fingers and toes. He had been hospitalized a month previously, and treatment had consisted of two blood transfusions and streptomycin, about 20 injections, according to the patient.

Physical examination on his admission to the hospital revealed a seriously ill, lethargic man with extreme hoarseness and difficulty in phonation. He had a florid generalized eruption and marked edema of the face and extremities. Lesions in all stages of involution and evolution were noted. There were gray-brown macules at the sites of preexisting lesions. There were scattered capillary telangiectases on the front and back of the thorax. There were several crateriform ulcers on the buccal mucosa, soft palate, and uvula, measuring up to 5 mm. in diameter and 3 to 4 mm. in depth. The anterior borders of the tongue were red and denuded. The lungs were clear to percussion and auscultation, except for some questionable dulness over the right upper lung fields. Individual lesions varied in size from a few millimeters to 6 cm. or more. Some of the lesions were superficial erythematous scaly plaques, some of which were infiltrated and some of which were rubbery deep-seated nodules of from bean to walnut size. There was generalized lymphadenopathy, most marked in the axillae.

Laboratory studies revealed the following: The urine showed a trace to 3+ reaction for albumin; a few white blood cells and occasional red blood cells were seen on microscopic examination. The hemogram disclosed 14.5 gm. of hemoglobin per 100 cc. and 5,460,000 to 3,200,000 red blood cells and 15,000 to 46,000 white blood cells per cubic millimeter, with 91% neutrophiles, 2% monocytes, and 7% lymphocytes. The total protein was consistently low and the albumin-globulin ratio reversed. Many sputum examinations showed no acid-fast organisms. The thymol turbidity was 10 units; the alkaline and acid phosphates were normal, and the serum bilirubin was less than 0.5 unit.

The results of sternal marrow examination were reported as follows: "The marrow is of average cellularity. The distribution of granulocytes and nucleated red blood cells appears normal. The neutrophiles display marked toxic granulation. There is an unusual number of macrophages—significance unknown. Careful search of two slides revealed none of the so-called lupus erythematosus cells."

A roentgenogram of the chest was reported as follows: "The chest shows evidence of pulmonary infiltration. There is a small area of pleural fibrosis in the right apex, and thickening of the interlobar fissure is present on the right."

Histological examination of a lesion on the left chest was reported as showing mycosis fungoides.

Treatment was mainly supportive. He was given steam inhalations, 3 units of plasma, 200 cc. of whole blood, procaine penicillin G (crysticillin®) 300,000 units intramuscularly every 12 hours, and vitamin E.

His condition remained essentially unchanged, except that the edema increased and the red and white blood cell counts decreased. There was respiratory obstruction, but examination of the larynx revealed the epiglottis to be normal, the pyriform sinuses clear with moderate edema of the arytenoid cartilage, and the false vocal cords markedly edematous. The cords were uneven and were covered with a white exudate. There was a small uneven nodule in the interarytenoid space. The airway was adequate. A bloody diarrhea developed, the respirations became more rapid and shallow, and the pulse rate increased. The patient died 20 days after admission to the hospital.

At autopsy the anatomical diagnoses, including histological findings, were (1) generalized mycosis fungoides (lymphoblastosis) of the skin, liver, lung, adrenal gland, and lymph nodes, (2) multiple benign polyposis of the descending colon, and (3) adenocarcinoma of the descending colon.

Histological examination of the skin revealed a somewhat increased amount of keratinization. The epithelial layer was infiltrated with large cells having clear cytoplasm and nuclei

that were darkly staining. The cells ranged from dark round cell types to larger cells of epithelioid character. Mitotic figures were seen only occasionally. In the deeper layers nests of the same type of cells were seen around the sweat glands and blood vessels. In a few areas these cells invaded the lumen of the blood vessels. The larger cells resembled "mycosis cells." The fibrous connective tissue appeared desmoplastic with increased amount of collagen. The histologist's impression was mycosis fungoides.

Histological examination of the colon showed the mucosa to be polypoid. The mucous glands were engorged and the nuclei small and vesicular. An increased number of lymphocytes was seen between the glands. Throughout the submucosa there were many anaplastic epithelial cells arranged in acini, several of which contained mucus. Several other sections revealed benign polypoid formation. The histologist's impression was adenocarcinoma of the sigmoid colon and multiple polyposis.

COMMENT

In a careful search of the literature Beerman and Thomas [1] found that only rarely is mycosis fungoides simultaneously associated with other diseases. In reviewing 136 cases of mycosis fungoides reported in the literature, Jordan and Areschewa [2] found that 38 cases terminated fatally. Death was due to cachexia in 10; probable roentgen-ray damage in 10; metastases to internal organs in 4; lung, heart, brain, or endocrine gland complications in 5; intercurrent disease in 1, and unstated causes in 8. It is noteworthy that in none was there evidence that carcinoma was the cause of the fatal termination.

The case of a 58-year-old Russian-born woman was presented by Skeer.[3] She had an eruption of the breasts, back, chest, upper abdomen, and pubic region of three months' duration. The eruption consisted of numerous round and oval erythematous lesions, slightly infiltrated, with fine scales, and of varying shades of red. She had, in addition, carcinoma of the sigmoid colon near the splenic flexure with intussusception. The resected portion of the tumor revealed adenocarcinoma. In discussing his case, Skeer stated that there was little in the literature associating carcinoma with mycosis fungoides, either directly or coincidentally.

Gold [4] reported the case of a 75-year-old man who had been under observation for 11 years. He was originally treated for carcinoma of the scrotum by surgical excision, and subsequently, right inguinal gland involvement was treated surgically and by deep roentgen irradiation. Follow-up showed no recurrence, although he had been hospitalized three years previously for left inguinal lymphadenopathy which, however, did not prove to be carcinomatous. One year later an irritable red eruption suddenly appeared on both legs and soon spread to involve the arms and back. These areas bled easily on the slightest trauma. The irritation, marked at the onset, had been absent for several months. The extent of the eruption seemed to be decreasing at the time of presentation, and the patient stated that areas formerly involved had returned to normal. On examination there were symmetrical, well-circumscribed, deep red, nonindurated, and slightly scaly plaques. On the trunk the lesions were devoid of scales, and there were areas of normal skin within the abnormal areas. There was no lymphadenopathy, splenomegaly, or hepatomegaly.

1. Beerman, H., and Thomas, C. C.: Mycosis Fungoides Developing in a Patient with Congenital Ichthyosiform Erythroderma, J. Invest. Dermat. **7**:271 (Dec.) 1946.

2. Jordan, A., and Areschewa, W.: Das Schicksal der Kranken mit Mycosis fungoides (M.f.), Dermat. Ztschr. **74**:126 (Oct.) 1936.

3. Skeer, J.: Mycosis Fungoides in a Patient with Carcinoma of the Colon, Arch. Dermat. & Syph. **47**:860 (June) 1943.

4. Gold, S.: Mycosis Fungoides, Brit. J. Dermat. **62**:179 (April) 1950.

There was a marked radiodermatitis of the right groin. An area over the left forearm had been treated with four weekly applications of 100 r of superficial roentgen rays without notable response. On histological examination the epidermis showed loose hyperkeratosis and patchy parakeratosis with atrophy of the Malpighian layer. There was a dense infiltrate lying immediately under the epidermis and extending along the blood vessels, which consisted of large and small round cells, plasma cells, polymorphonuclear cells, and numerous mononuclear and polynuclear reticulum cells. A few mitotic figures were seen. The stroma of the infiltrate was provided by argyrophil fibers. The histological picture was characteristic of mycosis fungoides.

A 68-year-old man, reported on by Hughes,[5] first noted red scaly patches on the front of the legs, extending from just below the knees to 1 in. (2.5 cm.) above the ankles. Severe itching of these areas prevented the patient from concentrating on his work and disturbed his sleep. The eruption gradually spread to the trunk, limbs, scalp, and face, and within six months there was severe exfoliative dermatitis with intractable pruritus. After one month in the hospital he was discharged much improved, with some residual pruritus at night, a red hue to the skin, and areas of small scaly patches on the trunk. Three months later a nodule appeared on the back of the left hand. This lesion was excised, and the histological report was epithelioma. Later, subcutaneous nodules appeared on the backs of both hands and forearms. These nodules gradually increased to the size of marbles. The following month the pruritus recurred. Therapy consisted of vitamins, antihistamine, and a course of dimercaprol. Improvement was noted in the skin, which no longer scaled, and the pruritus disappeared. However, the redness and induration remained.

Hynes and Wintrup [6] reported an associated squamous-cell carcinoma of the face in a case of mycosis fungoides.

A case of poikiloderma atrophicans vasculare with changes of mycosis fungoides, basal-cell epithelioma, and squamous-cell epithelioma was reported by Leavell and associates.[7]

The patient reported on by Beerman and Thomas [1] was a Negro woman who had, during a period of more than 20 years, a series of seven neoplastic and ectodermal abnormalities as follows: ovarian cyst, fetal adenoma of the thyroid, congenital ichthyosiform erythroderma, uterine tumor, carcinoma of the uterine cervix, mycosis fungoides, and adenocarcinoma of the rectum.

SUMMARY

Two cases are reported in which there was a simultaneous occurrence of mycosis fungoides and carcinoma.

A short review of cases reported in the literature of the association of mycosis fungoides and carcinoma is presented. From these reports in the available literature it is concluded that this association is not common.

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5. Hughes, P.: Mycosis Fungoides, Brit. J. Dermat. **62**:414 (Oct.) 1950.

6. Hynes, J. F., and Wintrup, C. K.: Mycosis Fungoides, Delaware M. J. **18**:83 (April) 1946.

7. Leavell, U. W.; Stewart, J. J., and Thomsen, J. G: Poikiloderma Vasculare Atrophicans with Changes of Mycosis Fungoides; Basal Cell Epithelioma; Squamous Cell Epithelioma, Arch. Dermat. & Syph. **61**:529 (March) 1950.

SIGNIFICANCE OF ACANTHOSIS NIGRICANS

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ACANTHOSIS nigricans is significant not only to dermatology; its ramifications and associations extend to many branches of medicine. This paper elaborates on aspects of acanthosis nigricans which are of interest to various medical disciplines.

Two types of acanthosis nigricans, a dermatosis benign in itself, are observed. The type associated with cancer of an internal organ is because of this association called "malignant." The type of the dermatosis not so associated is called "benign." The quotation marks denote that it is illogical to differentiate the two types by such qualifications. The terms "malignant" and "benign" have, however, been retained for practical reasons. These designations are far more satisfactory than the terms "adult" and "juvenile," since children may suffer from and die of "malignant" acanthosis nigricans, while otherwise healthy, older persons have suffered from "benign" acanthosis nigricans for many years.

"Benign" acanthosis nigricans begins at birth or in childhood or appears at puberty. In any case, it becomes accentuated during the adolescent period. When adolescence is over, the dermatosis either regresses or remains stationary.

"Malignant" acanthosis nigricans can occur in children. Most of the patients, however, show the first signs as adults. Cutaneous involvement may precede internal cancer, may follow it, or may coincide with manifestations of the tumor. Occasionally, one sees temporary improvement following treatment of the cancer. With the recurrence of the tumor or the appearance of metastases, the cutaneous lesions again become prominent.

The two types show enough differences to justify considering them as separate diseases. They are activated by different principles. They occur in different age groups. They may follow different genetic mechanisms.[1] Each form stays within its pattern in the individual patient, and whenever there is familial involvement all family members show the "benign" type. Perhaps the best proof of the separate character of "benign" and "malignant" acanthosis nigricans is the fact that adults suffering from "malignant" acanthosis nigricans passed through puberty without displaying "benign" acanthosis nigricans.

The twofold incidence of the disease, a unique phenomenon in medicine, offers material for comparative analysis of many phases of the problem. Points for comparison are the dermatoses (Fig. 1, *Left*) *A* and *a*; the inciters *B* and *b*, and the relationships *C* and *c* between dermatoses *A* and *a* and inciters *B* and *b* or the modes of action of the inciter of each type. The fact that acanthosis nigricans occurs

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1. A separate paper will deal with the genetics of acanthosis nigricans.

in both sexes again presents double information, this time on the inciters of the "benign" type (B_1 for the males and B_2 for the females) which are different in each sex.

It is through its relationship to cancer, however, that the dermatosis becomes important. Association with cancer occurs in 100% of cases of "malignant" acanthosis nigricans. This is remarkable if one realizes that no other benign disease, cutaneous [1a] or otherwise, is indicative of internal cancer. The significance to cancer research of this dermatosis, visible and recognizable at an early state, is, therefore, obvious.

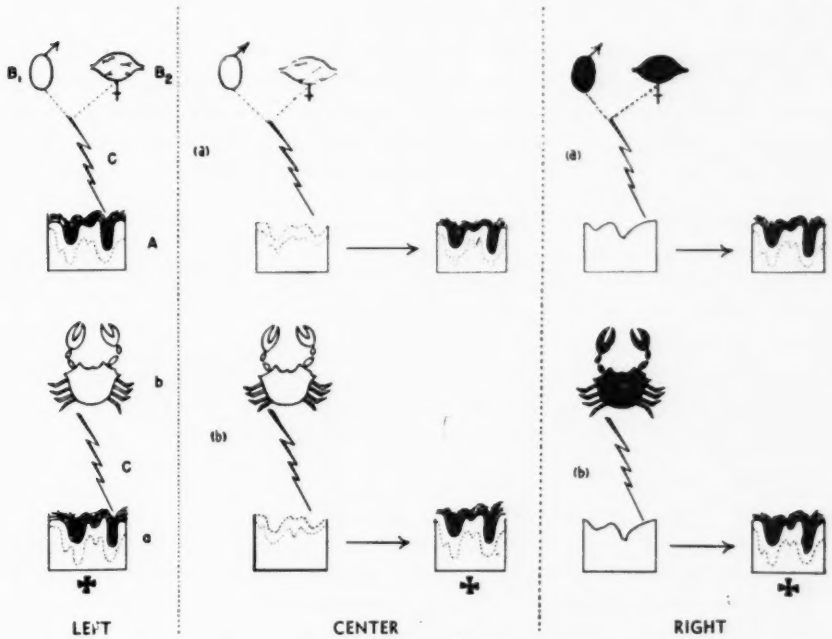

Fig. 1.—Left, twofold incidence of the dermatosis. *A* represents "benign" acanthosis nigricans; *B* is the inciter of the "benign" type of the disease in males, and B_2 is the inciter in females; *C* is the relationship between *A* and B_1 and B_2. "Malignant" acanthosis nigricans is represented by *a*; *b* is the inciter (a cancer factor) of the "malignant" type of the disease, and *c* is the relationship between *a* and *b*. Center, for the production of acanthosis nigricans predisposed skin may be necessary to react characteristically when stimulated by the activators of "benign" acanthosis nigricans (*a*) and "malignant" acanthosis nigricans (*b*). Right, for the production of acanthosis nigricans specific inciters may be necessary which activate the normal skin in "benign" acanthosis nigricans (*a*) and in "malignant" acanthosis nigricans (*b*).

SIGNIFICANCE OF ACANTHOSIS NIGRICANS IN CANCER RESEARCH

1. *A Dermatosis in Man Duplicating Conditions Produced in Test Animals.*—

One great advantage of animal experiments for cancer research is the controlled production of tumors either in highly susceptible strains or after inoculation of

1a. Lately, the association of neoplasms with two other dermatoses, dermatomyositis and dermatitis herptiformis, has frequently been described.

tumor material. Not all conclusions derived from animal cancer, however, are valid for man. An inbred cancer-susceptible population does not exist, nor is it feasible to carry out transplantation experiments on human beings. The appearance of cancer, however, can be predicted with certainty in the patients suffering from "malignant" acanthosis nigricans whose cutaneous lesions precede any signs of cancer. Such patients comprise about 20% of all those with "malignant" acanthosis nigricans. The potentiality of these patients for development of internal cancer is 100%, and the time which elapses before cancer appears may be several years. These two circumstances should prove of great value in experimental studies on early cancer changes in the body. Results of these studies may be important for cancer research in general and for acanthosis nigricans in particular. They may determine whether cancer is but the activator of the cutaneous lesions or is in some way, perhaps genetically, connected with acanthosis nigricans.

2. *Role of Hormonal Imbalance in Activation of "Benign" and "Malignant" Acanthosis Nigricans.*—Activation of the "malignant" type of acanthosis nigricans by cancer seems to be proved in the instance of a recurrent or metastasizing cancer which has been, apparently, successfully treated. After treatment of cancer by surgical or other means, the cutaneous lesions may subside or even disappear. They, however, invariably reappear with renewed signs of cancer activity.

The spontaneous exacerbation of "benign" acanthosis nigricans at puberty and the regression of the cutaneous lesions after adolescence favor the assumption that a factor connected with adolescence is responsible for the activation of "benign" acanthosis nigricans. A similar activating effect by estrogen was demonstrated by Davis, Boynton, Ferguson, and Rothman,[2] who caused pigmentation to appear in women in areas which physiologically possessed the faculty of pigment formation. Preliminary studies have not disclosed any abnormal steroid hormones in young persons with "benign" acanthosis nigricans. There is, however, evidence that the physiologic imbalance of the steroid hormones at puberty is the decisive factor in activation of the dermatosis. When this period of imbalance is over, the cutaneous lesions may subside. If one could determine that the steroid hormones are activators of "benign" acanthosis nigricans, then this fact might point to the role of a specific hormonal imbalance connected with cancer as activator of the "malignant" type.

3. *Recognition of Certain Adenocarcinomas as a "Biologic" Group.*—Former surveys [3] on cancer associated with acanthosis nigricans have shown the homologous qualities of these tumors. Although they may originate in various organs, they all are adenocarcinomas. This type of tumor has been evident in almost all instances either in the primary growth or in the metastatic tumor. My last statistics [3] revealed that 92% of tumors originated in the stomach or abdominal cavity and 8% in breast, lung, etc. These figures will have to be revised to show a higher

2. Davis, M. E.; Boynton, M. W.; Ferguson, J. H., and Rothman, S.: Studies on Pigmentation of Endocrine Origin, J. Clin. Endocrinol. **5**:138-146 (March) 1945. The Role of Estrogens in Physiologic Hyperpigmentation, editorial, J. A. M. A. **128**:734 (July 7) 1945.

3. Curth, H. O.: (*a*) Cancer Associated with Acanthosis Nigricans, Arch. Surg. **47**:517-552 (Dec.) 1943; (*b*) Acanthosis Nigricans and Its Association with Cancer, Arch. Dermat. & Syph. **57**:158-170 (Feb.) 1948; (*c*) Acanthosis Nigricans und Krebs, Ztschr. Krebsforsch. **56**:307-328, 1949.

percentage of lung cancer because of recent increases in bronchial carcinomas observed in association with acanthosis nigricans.[4] This increase coincides with an increase in lung cancers reported generally.

The cancers associated with acanthosis nigricans are highly malignant. They are characterized by early metastasis or inoperability. Their mortality rate is 100%. The average duration from discovery to death, previously reported as 11.9 months, appears shorter in the much smaller series of cases reported in this paper.

Clemmesen,[5] of the Danish Cancer Registry, has emphasized the fact that the adenocarcinomas associated with acanthosis nigricans seem to function as a "biologic" group. They occur in various organs, but the fact of their association with acanthosis nigricans makes them one group. Previously, evidence that certain adenocarcinomas could be considered as a group has come from pedigrees with a significantly high incidence of various adenocarcinomas. Warthin[6] and Hauser and Weller[7] reported on the incidence of adenocarcinomas in members of one family, and Jacobsen,[8] Busk,[9] and Wassink[10] found high incidence of adenocarcinomas of various organs in the near relatives of probands[11] suffering from mammary cancer.

Whether cancers associated with acanthosis nigricans can be considered as representative of adenocarcinoma in general or as constituting a group within a group will depend largely on the outcome of further studies on the inherent qualities of these carcinomas, such as their biochemical properties. There is some evidence that cancers associated with acanthosis nigricans are different from cancers not so associated. It seemed to me that adenocarcinoma in relatives of patients I observed was not so highly malignant as that occurring in the patients themselves. In one case of malignant (?) acanthosis nigricans (Case 2), one sister of the father of the proband survived a uterine cancer and lived to have a primary gastric adenocarcinoma. It can be assumed that if her first cancer had been highly malignant she would not have lived many years before manifesting another cancer. In the family of a patient with "benign" acanthosis nigricans (J. B.) the duration of three cancers occurring in family members was in each instance much longer than the average 12 months of the cancer associated with acanthosis nigricans. The patient's mother, aged 34, died of rectal cancer of four years' duration. Her paternal uncle, aged 78, is alive, six years after gastrectomy for cancer. The daughter of this man died at the age of 48 of cancer of the lung, four years after its onset.

4. Ellenbogen, B. K.: Acanthosis Nigricans Associated with Bronchial Carcinoma: Report of 2 Cases, Brit. J. Dermat. **61**:251-254 (July) 1949.

5. Clemmesen, J.: Personal communication to the author.

6. Warthin, A. S.: The Further Study of a Cancer Family, J. Cancer Res. **9**:279-286 (June) 1925.

7. Hauser, I. J., and Weller, C. V.: Further Report on Cancer Family of Warthin, Am. J. Cancer **27**:434-449 (July) 1936.

8. Jacobsen, O.: Heredity in Breast Cancer: A Genetic and Clinical Study of 200 Probands, Copenhagen, Nyt Nordisk Forlag, Arnold Busck, A. S., 1946.

9. Busk, T.: Some Observations on Heredity in Breast Cancer and Leukemia, Ann. Eugenics **14**:213-229 (Nov.) 1948.

10. Wassink, W. F.: Cancer et hérédité, Genetica **17**:103-144, 1935.

11. A proband or propositus is an affected individual who has come to the attention of an investigator, who thereupon studies the individual's pedigree.

If, on the other hand, one considers that the cancer of the family members and that of the patient with acanthosis nigricans belong to one and the same group, one has to conclude that the presence of acanthosis nigricans or some other factor connected with the dermatosis increases the malignancy of the tumor.

4. *Explanations of the Rarity of Acanthosis Nigricans.*—In an endeavor to detect early cases of "malignant" acanthosis nigricans, 116 patients with advanced cancer of various types were studied at the Montefiore Hospital, New York, with the cooperation of Dr. D. Laszlo. No instance of acanthosis nigricans was seen. I was informed, however, that a former patient who could not be reexamined had suffered from acanthosis nigricans. Because of the possible diagnostic significance of acanthosis nigricans, examination of the axillae is now a routine measure at this hospital.

The rarity of acanthosis nigricans in this survey, as well as in the general population, has remained a striking phenomenon. In comparing the great number of cases of adenocarcinoma with the small number of instances of "malignant" acanthosis nigricans, one arrives at the conclusion that for the production of acanthosis nigricans one may need a type of skin predisposed to react characteristically when stimulated by a special activator. Of the victims of adenocarcinoma, only those with such skin will respond with "malignant" acanthosis nigricans (Fig. 1, *Center, (b)*), and only those adolescents whose skin is capable of producing acanthosis nigricans will show the "benign" form (Fig. 1, *Center, (a)*). One method of proving such a cutaneous specificity would be to find evidence of genetic predisposition to acanthosis nigricans; one method of disproving it is to find biochemical differences between adenocarcinomas with and adenocarcinomas without "malignant" acanthosis nigricans, or between the steroid hormones of patients with and those of persons without "benign" acanthosis nigricans.

If, however, the specificity lies in the inciter rather than in the skin, it is possible that anyone with a normal skin who produces the specific activator will have acanthosis nigricans (Fig. 1, *Right*). Inheritance of acanthosis nigricans would then consist of an inherited tendency toward development of abnormal inciters.

There is another hypothetic explanation of the rarity of "malignant" acanthosis nigricans, i. e., the assumption that more instances of the dermatosis would be seen if victims of adenocarcinoma remained alive long enough to display acanthosis nigricans. In favor of this idea are the observations that in some cases acanthosis nigricans appears rather late after manifestation of cancer, and that patients suffering from cancer associated with acanthosis nigricans do not live long as a rule. Most of the adenocarcinomas occurring in the general population, however, do not seem to belong to the well-defined group of adenocarcinomas associated with acanthosis nigricans.

5. *Does the Patient Suffering from "Benign" Acanthosis Nigricans Remain Free from Cancer?*—"Benign" acanthosis nigricans has been defined as a specific dermatosis which lacks the association of internal adenocarcinoma. It is reasonable to inquire whether the patient with "benign" acanthosis nigricans will remain free from the specific adenocarcinoma associated with "malignant" acanthosis nigricans or from cancer at any age and in any form.

"Benign" acanthosis nigricans does not prevent squamous-cell carcinoma; on the contrary, pigmented nevi occurring together with "benign" acanthosis nigricans

can easily assume characteristics of a nevocarcinoma. Pautrier and Hugel's [12] patient eventually exhibited this complication. Squamous-cell or nevoepithelioma, however, is different from the alveolar type of cancer with which I am here concerned.

Many patients with "benign" acanthosis nigricans, and their families, will have to be observed throughout their lifetimes before freedom from cancer of the patient with "benign" acanthosis nigricans can be established. Reports from the literature do not help since (1) I considered all instances of acanthosis nigricans in which occurrence of cancer was mentioned in the original or subsequent reports as belonging to the "malignant" type (in these cases, exacerbation of the cutaneous lesions at the time of the manifestation of cancer had been stressed) and (2) previous authors have not conducted follow-up studies on their patients with "benign" acanthosis nigricans.

6. *Does Acanthosis Nigricans Demonstrate That a Disposition to Cancer as Such Exists?*—Clemmesen [6] believes that acanthosis nigricans furnishes significant material for the answer to this question. In "malignant" acanthosis nigricans the location of adenocarcinoma may indeed vary from case to case. There is no proof, however, that in the individual patient with acanthosis nigricans the disposition to adenocarcinoma as such exists and not the disposition to the specifically located tumor.

SIGNIFICANCE OF ACANTHOSIS NIGRICANS IN DERMATOLOGY

1. *Determination of the Differences of the Two Types of Acanthosis Nigricans.*—The prognosis of the dermatosis depends on the type to which a case belongs. For purposes of clarification, even though it may oversimplify matters, one can state that "benign" acanthosis nigricans is a blemish, while "malignant" acanthosis nigricans is fatal.

The type of the dermatosis can be determined by analyzing its behavior. For this consideration two clinical data seem important: first, the age at which the dermatosis has begun, and, second, its course.

Age: One may cautiously summarize the age distribution of the two types of acanthosis nigricans as follows: A young person whose cutaneous changes have started before or at puberty is likely to be suffering from "benign" acanthosis nigricans. One should keep in mind, however, that in some cases the "malignant" disease has begun in childhood and youth. One is faced with "malignant" acanthosis nigricans if the dermatosis starts after puberty.

Course: Progression of the dermatosis occurs in childhood and at periods of activity of the specific activators, presumed, in the one instance, to be factors connected with the steroid hormones and, in the other, to be factors pertaining to cancer.

In "benign" acanthosis nigricans regression has been observed following the peak of adolescence. The lesions may disappear completely or may become fainter. In "malignant" acanthosis nigricans, temporary regression of cutaneous lesions is seen following temporarily successful treatment of the accompanying malignant tumor.

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12. Pautrier, L. M., and Hugel, G.: Maladie nævique généralisée à type de dystrophie papillaire et pigmentaire (acanthosis nigricans) et de nævi pigmentaires et verruqueux disséminés sur tout le corps, Bull. Soc. franç. dermat. et syph. **29**:81-91, 1922.

Patients in whom the first cutaneous signs of acanthosis nigricans were observed even shortly after puberty were suffering from the "malignant" type. This was noted in females having "malignant" acanthosis nigricans for whom data on first menstruations were given. During menarche no cutaneous activity was observed.

Short résumés of cases of acanthosis nigricans illustrate how analysis of the two factors, age at onset of cutaneous changes and course of the dermatosis, determines the type of acanthosis nigricans. I have learned of these cases from many physicians interested in the problem who have given me permission to study the pedigrees and publish the data on their patients.

Cases of "Malignant" Acanthosis Nigricans: Case 1.—J. Z., a patient of Dr. A. Hollander, Springfield, Mass., and Dr. C. Guy Lane, Boston, was a 26-year-old man. There is conflicting information concerning the time of onset of the dermatosis. Records of the two dermatologists and of the Mercy Hospital, Springfield, Mass., place the beginning of dark, verrucous changes in the body folds in his 25th year. His surviving sister, however, told me that she believes her brother had been aware of "dark" axillae as a young boy. All reports agree on the rapid dissemination of the dermatosis over almost the entire body simultaneously with loss of weight, weakness, and signs of a malignant tumor. In the hospital, paralysis of the lower and upper

Behavior of "Malignant" Acanthosis Nigricans at Time of Menarche

Author *	Patient's Age, Yr.	Location of Cancer	Menarche	Duration of Acanthosis Nigricans	Duration of Cancer
Spietschka	20	Chorionic carcinoma	At 14 yr.; menses regular	Over 16 mo. lesions disappeared after operation but have recurred during past 2-3 mo.	21 mo.; apparently postoperative cure; later metastases
Flaskamp	23	Gastric	At 14½ yr.; menses regular	About 9 wk.	Several months
Jakubson	27	Gastric	At 17 yr.; menses ceased 5 mo. before death	2 yr.	5 mo.

* Spietschka, T.: Arch. Dermat. u. Syph. **44**: 247-276, 1898. Flaskamp, W.: Ztschr. Krebsforsch. **21**: 369-386, 1923-1924. Jakubson, A.: Russk. klin. **8**: 781-792, 1927; abstracted, Zentralbl. Haut- u. Geschlechtskr. **28**: 279, 1929.

extremities and loss of control of bowel and bladder function were noted before death at the age of 26. At autopsy gastric carcinoma with widespread metastases including the left adrenal gland was found. Histologically, the stomach showed a highly malignant neoplasm disrupting the mucosa, composed of undifferentiated polygonal and spheroidal cells, growing loosely with very little attempt at any organized pattern. There was a good deal of pleomorphism of the cells, many of which were seen invading the underlying coats.

Case 2.—L. B., a patient of the late Dr. Dudley Smith, Charlottesville, Va., is a 28-year-old blonde woman. Menarche occurred at 13. The patient has two daughters, born in 1943 and 1946. In February, 1945, a pregnancy ended in abortion at three months. About this time discoloration of the inner aspects of the thighs, the back of the neck and the axillae was noted. A diagnosis of acanthosis nigricans was made at the University of Virginia Hospital, and search for a tumor was begun. At an operation performed by Dr. J. K. Kaufman, of Murfreesboro, Tenn., and Dr. Burnett Wright, of Nashville, Tenn., a rudimentary left kidney and an enlarged left adrenal gland were seen. No malignant changes were present in the rudimentary kidney or in the abdomen. The cutaneous lesions progressed, and in 1948 the patient returned to the University of Virginia Hospital. Intensive observation disclosed no tumors of the gastrointestinal or urogenital tracts, breasts, lungs, or other organs. In January, 1949, the patient was observed by me at Presbyterian Hospital, New York, and the absence of cancer was confirmed. The cutaneous changes were typical of the dermatosis. In June, 1950, roentgen examinations performed by Dr. McClure, of Nashville, Tenn., disclosed a normal gastrointestinal tract. In April, 1951, the patient complained of severe pain in the left side. On May 1, Dr. J. K. Kaufman and Dr. L. M. Kennedy, of Murfreesboro, Tenn., performed a total hysterectomy, bilateral salpingo-

oophorectomy, and appendectomy. The left ovary was cystic, and there was a moderately large parovarian cyst. The uterus was moderately enlarged and showed scars from an old cervicitis. Careful exploration disclosed no signs of abdominal cancer. The extent of the dermatosis has not changed after the second operation.

Case 3.—P. D., a patient of Dr. Henry E. Michelson, Minneapolis, was a 51-year-old woman who had first noticed dark pigmentation of the skin in August, 1947. The eruption spread slowly, and by February, 1948, pigmentation and papillomatous warts had involved the axillae, groins, and areas under the breasts and about the neck and were almost generalized. Involvement of lips, mouth, and eyelids was noted. The mucous membranes of the mouth showed edema and diffuse papillary erosion of the hard palate. Hyperkeratosis of the palms and soles appeared. Simultaneously with the onset of cutaneous disease, epigastric distress and loss of weight were noted. In March, 1948, a laparotomy performed at the University of Minnesota Hospital, Minneapolis, disclosed an inoperable gastric carcinoma. The patient died of adenocarcinoma of the stomach with extensive intra-abdominal and peritoneal metastases 10 months after onset of her symptoms. During the last months of her life the verrucous and papillary growths increased in size and number.

Case 4.—H. D., a patient of Dr. P. W. Spear,[13] Brooklyn, was a 50-year-old man who had noticed increasing darkness of the axillae, the nipples, and the skin around the neck for two months. One month later, he began to complain of sharp pain across the anterior portion of the midchest, cough and shortness of breath on exertion, and loss of weight. The patient died three months after onset of cutaneous signs. Autopsy at the Veterans Administration Hospital, Manhattan Beach, Brooklyn, revealed acanthosis nigricans and anaplastic carcinoma of the right lung, with involvement of the bronchial lymph nodes.

Case 5.—H. W. V., a patient of Dr. H. D. Shatin, of the Veterans Administration Hospital, Bronx, N. Y., was a 50-year-old man who was suffering from bronchial (?) carcinoma which had begun with persistent cough five and a half months prior to hospitalization. During his hospital stay, mild grayish discolorations and thickening and roughening of the skin were noted in the axillae, inguinal folds, and antecubital areas and on the dorsa of the feet and the anterior aspects of both legs. A biopsy specimen from the left axilla revealed acanthosis nigricans. A biopsy section from a node in the left supraclavicular area showed metastatic carcinoma, the origin of which was thought to be bronchiogenic but could not be determined with certainty. Gynecomastia and edema of the legs developed. Roentgenograms of the gastrointestinal tract did not disclose a malignant tumor. However, there was considerable displacement of the stomach by a large para-aortic retrogastric mass, and the liver and spleen were enlarged. Nontender movable nodes were felt in the cervical, axillary, and inguinal regions. Roentgenograms of the chest disclosed nodulations in the right paratracheal and right paracardiac regions. There were infiltrations over the right base with pleural thickening in the axillary segments in that region. There were also a rounded opacity with a diameter of about 3 cm. in the left paracardiac region and another one just below it. The patient died seven and a half months after the first signs of malignant tumor became apparent and a few weeks after acanthosis nigricans had begun.

Case 6.—M. S., a patient whose history was obtained from Dr. J. Victor Greenebaum, Cincinnati, was a woman in her seventies. Several years prior to her death a peculiar brownish or blackish discoloration in the axillae, groins, and the suprapubic and perineal regions was noted. A diagnosis of acanthosis nigricans was made by several dermatologists. At the onset of the slowly spreading dermatosis, extensive search for a malignant tumor was undertaken but yielded no results. In 1946, however, a mass appeared in the upper left side of the abdomen. In July, 1947, the patient died and autopsy revealed acanthosis nigricans, gastric adenocarcinoma, and metastatic adenocarcinoma of the liver, uterus, and many lymph nodes.

Case 7.—S. S., a patient of Dr. J. Y. Feinstein, Minneapolis, was a 66-year-old man, who in 1946 showed increasing signs of acanthosis nigricans. One year later cachexia set in. Exploratory operation in July, 1947, by Dr. O. H. Wangensteen, at the University of Minnesota

13. This case, which was previously published (Spear, P. W.: Acanthosis Nigricans Associated with Cancer of the Lung, J. Thoracic Surg. **20**:304-309 [Aug.] 1950), has been included here because Dr. Spear gave me permission to investigate the pedigree.

Hospital, Minneapolis, disclosed an adenocarcinoma of the sigmoid colon (Dukes Class C), with metastases to the regional lymph nodes, massive involvement of both lobes of the liver, and periaortic nodes. At that time roentgenograms of the chest revealed probable carcinomatous metastases in the left lung. Two years after the onset of cutaneous signs the patient died. No autopsy was performed.

Case 8.—E. H., a patient of Dr. Charles D. Hershey and Dr. Howard Phillip Sr., Wheeling, W. Va., was a 36-year-old woman. The first cutaneous changes appeared in the summer of 1947 during pregnancy. She delivered in the fall of 1947, and the characteristic skin changes increased. In February, 1948, a gastric carcinoma was diagnosed on the basis of roentgenograms. At the operation Dr. Charles D. Hershey noted that the serosal surface had a peculiar grayish color which he had never seen before. The patient had an uneventful recovery, and the cutaneous lesions began to subside rapidly after removal of the stomach. One or two months later they were very faint. The patient did well for about two months, but five months after operation she showed signs of extensive abdominal metastases. She died approximately six months after operation. Acanthosis nigricans had become prominent again during the two or three months prior to her death.

Case 9.—L. W., a 43-year-old man, has been a patient of Dr. J. C. Pease,[14] of the United Oxford Hospital, The Radcliffe Infirmary, Oxford, England. In August, 1945, darkness of the patient's skin was commented upon. The skin became progressively darker, rougher, and drier, and the body folds, other large areas of the extremities and trunk, and lastly the oral cavity were involved. During the summer of 1949, the patient started to complain of pain in the left side of the chest. Roentgenograms disclosed a tumor of the upper lobe of the left lung. A provisional diagnosis of left bronchial carcinoma was made. At the time of the last note from Dr. Pease, the patient was progressively getting worse.

Case 10.[15]—M. B., a 66-year-old woman, was a patient of Dr. H. Burstein, Decatur, Ill. In July, 1941, she started to complain of stomatitis, loss of weight, and increasing darkness and roughness of the body folds. A diagnosis of acanthosis nigricans was made, with which Dr. F. E. Senear, of Chicago, concurred. In January, 1942, a firm, enlarged, left supraclavicular node was removed for biopsy, and a diagnosis of adenocarcinoma, Grade III, was made by Dr. A. C. Broders, of the Mayo Foundation, Rochester, Minn. The patient died in February, 1942. No autopsy was performed.

Comment: In all these cases, with the exception of Case 2, the association of the dermatosis with a malignant tumor has been established. The onset of the cutaneous lesions occurred at varying times after puberty in all patients with the possible exception of one (Case 1). In this patient involvement of the axillae may have commenced before puberty. In this patient, as well as in the others, however, exacerbation of existing lesions took place not at puberty, but later. The patients' ages at onset of the dermatosis ranged from 25 to the seventies, with the possibility that in the first patient (Case 1) onset may have been during childhood or youth. The average age at onset was 48.3 years.

14. This case will be published in more detail by Dr. Pease.

15. After completion of this paper, I learned of several new cases of "malignant" acanthosis nigricans. A 66-year-old woman was referred to me by Dr. G. McNeer, of Memorial Hospital, New York. The patient had extensive progressive changes of the body folds, palms, and mucous membranes of seven months' duration. At an exploratory laparotomy, performed at Memorial Hospital, diffuse abdominal carcinomatosis originating from gastric (?) adenocarcinoma was seen. Many details of this case are similar to an observation on a man of 68 years by M. Berke and F. B. Wilkins (The Surgical Significance of Acanthosis Nigricans, Ann. Surg. **132**:980-985 [Nov.] 1950). Through the courtesy of Dr. A. B. Peacock and Dr. H. Beerman, Philadelphia, I saw a 69-year-old diabetic woman suffering from progressive acanthosis nigricans of body folds, palms, and mucous membranes of eight months' duration. She was jaundiced, and a liver biopsy revealed adenocarcinoma which was probably primary in the gall bladder.

Case 2 has been placed in this group of cases of "malignant" acanthosis nigricans because onset of the cutaneous lesions at 24 years of age and constant progression of the dermatosis fulfill the criteria for "malignant" acanthosis nigricans. Furthermore, in this connection it should be emphasized that the patient did not show any cutaneous involvement at puberty.

In all cases in which a malignant tumor was manifest there was progression of the cutaneous changes. In Case 1 the cutaneous lesions may have been quiescent for years, until at the age of 25 exacerbation of the skin lesions set in. Disappearance of cutaneous lesions following removal of the tumor was reported in Case 8. The cutaneous changes, however, reappeared a few months later. Inasmuch as in similar instances the tumor has always recurred or metastasized at about the time the cutaneous lesions recurred, reappearance of "malignant" acanthosis nigricans seems to denote renewed cancer activity.

In two cases, Cases 2 and 8, pregnancy occurred in the course of "malignant" acanthosis nigricans. I have not personally observed these or other women suffering from acanthosis nigricans during gestation, but have gathered from the reports of the attending physicians that the cutaneous process progressed at about the same rate as during periods that patients were not pregnant. The dermatosis may have started during pregnancy, but the possibility exists that these women were more closely and more frequently examined at that time than they ordinarily were, with the result that slight cutaneous changes were discovered. It seems from the reports that during gestation the progression of acanthosis nigricans is not so rapid as that of malignant melanoma.

The further information which can be gained from these cases is that acanthosis nigricans and cancer started at about the same time in Cases 1 (?), 3, 4, and 10. In Case 5 acanthosis nigricans appeared after manifestation of the malignant tumor. I can state from personal knowledge of the case that diagnosis of the early cutaneous changes, which appeared as grayish, elevated lichenifications simulating neurodermatitis, was difficult. The diagnosis of acanthosis nigricans in this instance, as well as in other cases, was verified histologically. In Cases 1 (?), 6, 7, and 8 acanthosis nigricans preceded cancer by months or years; in Case 6, by "several" years. In Case 2 six years has already elapsed without manifestation of a cancer.

The cancers were verified by operation or biopsy in Cases 1, 3, 5, 7, 8, and 10 and by autopsy in Cases 4 and 6. In Case 9 the diagnosis was made by roentgenogram. Histologically, adenocarcinoma was noted in Cases 3, 6, 7, and 10. The cells of the highly malignant carcinoma of Case 1 were undifferentiated. Anaplastic carcinoma of the lung was seen in Case 4.

Four of the nine cancers were gastric (Cases 1, 3, 6, and 8). Metastatic cancer was diagnosed in two cases (Cases 5 and 10). The origin in Case 5 was thought to be bronchial; in one case (Case 4) cancer of the lung was present; in another (Case 9) the signs indicated this diagnosis. In Case 7 cancer of the sigmoid colon was found.

The high malignancy of the tumor associated with acanthosis nigricans has again been demonstrated. All cases resulted in early death. After appearance of the cancer, the average duration of life was 8.7 months, which is even shorter than the 11.9 months computed from a previous and larger series of patients.[3a]

The discoloration of the serosal surface noted in Case 8 may denote the occurrence of acanthosis nigricans in the mucous membranes of the gastrointestinal tract.

Cases of "Benign" Acanthosis Nigricans: Case 11.—E. B., a 28-year-old single man, was referred to me by Dr. L. Babalian, of Portland, Maine. The patient was presented by Dr. Babalian before the New England Dermatological Society in 1945,[16] as showing "juvenile acanthosis nigricans and ichthyosis," and by me[17] at the November, 1950, meeting of the New York Academy of Medicine, Section on Dermatology and Syphilis, with the diagnosis of "'benign' acanthosis nigricans, mental deficiency." The mother of this patient has mild diabetes, and there are other persons with diabetes in the mother's family. In early childhood mental retardation, epileptic seizures, and occasional loss of consciousness were noted. No seizures occurred after the age of 15. The patient had poliomyelitis (?) when he was 12 years old. The first signs of a cutaneous eruption were seen on the shoulder blades when the patient was 3 months old. The rash then slowly spread over almost the entire body. There was much intensification between the ages of 7 and 10 years. When the boy was 12 years old, the face became involved. Dr. Babalian noted in 1947 that the scalp was thick, rough, and verrucous, but it seems almost free of involvement at present. Otherwise, there has not been much change lately. The entire body as far down as the genitals and upper part of the thighs is involved. On the trunk there are numerous papillary, dirty brownish-looking lesions which have become confluent and present an elevated, rough, dry, and thick surface. At places there are small stripes and larger areas of normal skin. The axillae have been transformed into areas of dry, hard, brownish to blackish elevations. The eyelids are covered by dense, pinhead-sized verrucous growths. Scattered over both cheeks are yellowish-brownish papillary lesions. The scalp shows some scattered pigmented moles. In the antecubital areas and from there downward, extending to the dorsal surface of the hands, faint grayish confluent papular lesions are visible. The nipples and umbilicus have been changed into thick, blackish hyperkeratotic masses. There are papular lesions around the anus. The mucous membranes of anus and mouth, however, are free. Dr. G. F. Machacek's histologic diagnosis for skin removed from the abdomen was epidermal nevus with morphology similar to that of acanthosis nigricans. In special investigations no malignant tumor was detected. The urine on one occasion showed a small amount of glucose. On the sugar-tolerance test, a slight delay in the elevation of the blood sugar was noted.

Case 12.—S. M. was referred to me by Dr. A. C. Cipollaro, who had presented the child with a diagnosis of benign acanthosis nigricans before the New York Dermatological Society in October, 1950.[18] The patient, an only child, was a 15-month-old blond boy. His mother had noticed that at birth the dorsa of the child's hands were rough. When the boy was 4 months old, the neck and axillae became thickened, rough, and grayishly discolored. The cutaneous process slowly spread from the neck toward the chin and from the hands to the antecubital areas. There was dusky black, rough, papillary hypertrophy in the axillae and in a circular arrangement on the neck. Less pronounced disturbances were seen in the antecubital areas and on the abdomen. Lips and eyelids were coarse, and hands and fingers were rough. He had keratoses of the palms and soles and showed large keratotic rhagades of the umbilicus. Lately, further progression of the dermatosis has been observed.

Case 13.—L. H. was referred to me by Dr. G. T. Pack, of Memorial Hospital, New York. The patient was a blond, rather obese boy of 16 who apparently had shown the first cutaneous changes at the age of 2½ years. The discoloration became more intense and slowly spread to the elbows, arms, and behind the knees. Dr. C. Jordan, of Stroudsburg, Pa., saw the boy when he was 5 years old, and Dr. J. Goldberg, of Plainfield, N. J., four years later. Both dermatologists diagnosed the condition as acanthosis nigricans. In 1948, when the boy was 14 years old, the eruption was at its height. At Memorial Hospital a biopsy specimen was taken from the right side of the abdomen and was reported as showing acanthosis nigricans. No malignant tumor or evidence of adrenal insufficiency was found on study.

16. Babalian, L.: Juvenile Acanthosis Nigricans and Ichthyosis, Arch. Dermat. & Syph. **55**:411 (March) 1949.

17. Curth, H. O.: Benign Acanthosis Nigricans; Mental Deficiency, A. M. A. Arch. Dermat. & Syph. **64**:516 (Oct.) 1951.

18. Cipollaro, A. C.: Benign Acanthosis Nigricans, presented before the meeting of the New York Dermatological Society, New York, Oct., 1950.

Since 1948 the cutaneous changes have regressed. I saw the patient for the first time in April, 1950. He was hospitalized in Presbyterian Hospital, New York, from June 23 to July 8, 1950. He showed grayish elevated cutaneous changes on the anterior aspect of the neck, the antecubital areas, extensor surface of the elbows and right arm extending to the right hand, and large areas of the abdomen. The periphery of the axillae was involved to about 5 cm. beyond the axilla proper, but clearing of the central areas was noted. There was an island of normal-appearing skin in the middle of the abdomen. The dorsa of the feet were dry and ichthyotic, and there were some patches of dry, rough skin behind both knees.

In Presbyterian Hospital the patient showed bilaterally positive Babinski reflexes and ankle clonus. He had had a shuffling gait for the past two years. A spinal tap gave normal results. A diagnosis of a disturbance of the spinal cord affecting the pyramidal tracts was made. This disorder was considered hereditary and degenerative, rather than based on any tumor process. Roentgenograms of the spine and those in search of a malignant tumor revealed no abnormality. Values for urinary estrogens varied between 9.37 and 11.77 γ in 24 hours, which is within normal limits, and those for the 17-ketosteroids ranged between 9.0 and 11.85 mg. per 24 hours, which is low. A biopsy specimen was taken from the left axilla. Dr. G. F. Machacek's diagnosis was benign papilloma or epidermal nevus with characteristics of acanthosis nigricans.

Case 14.—S. C., a 41-year-old Jewish man, was referred to me by Dr. J. S. Shapiro, of Paterson, N. J. The patient was presented by Dr. Fred Wise (for Dr. J. J. Greengrass) in 1939 at a meeting of the New York Dermatological Society,[19] with the diagnosis of acanthosis nigricans, and by me in April, 1948,[20] at a meeting of the New York Academy of Medicine, Section on Dermatology and Syphilis, with the diagnosis of acanthosis nigricans, "benign" type. He was born with normal skin. When he was about 12 years old, discoloration and roughness of the skin began and have involved almost the entire body. In addition, numerous pigmented moles appeared. The cutaneous disease was stationary for about 20 years and has slightly regressed during the past 10 years. During this time, however, several moles which had been nicked were removed by desiccation in order to prevent malignant degeneration. The patient married in 1948 and is the father of a healthy baby girl.

Large areas of the body, including the face and body folds, showed confluent, rough, dry, keratotic, brownish to blackish elevated furrows. The changes of the face were less pronounced. The anus showed involvement, but the genitals, tongue, mouth, scalp, palms, and soles were free. A large number of sessile or pedunculated moles were present on normal and abnormal skin (Fig. 2). They were (1) dusky-brown, flat, and smooth, (2) skin-colored and slightly papillomatous, or (3) darkly pigmented, pea-sized, and dry.

A biopsy was performed on the trunk, with removal of a mole and a portion of the diseased skin. Dr. G. F. Machacek made the diagnosis of epidermal nevus. No signs of an endocrine disturbance or of an internal cancer were found. The 17-ketosteroids were 11.8 mg. in 24 hours.

Case 15.—A. M. was observed in Vanderbilt Clinic. She was a 2-year-old girl of Syrian parents and the third child of a father who suffered from von Recklinghausen's disease (neurofibromatosis). The child was born with cutaneous changes in the body folds which slowly regressed. Recently, however, pigmented nevi appeared near the umbilicus. She showed sharply limited, elevated, hyperpigmented areas of increased furrows symmetrically over the neck, in the axillae, on the abdomen, behind the knees, and on the thighs, legs, antecubital areas, and dorsa of feet and hands. The scalp, nails, and mouth were free. The child was mentally retarded and was rated as having the mentality of a child of 9 to 12 months.

Roentgenograms of the bones disclosed rarefaction and marked general deformities characteristic of the atrophy of disuse. A search for a malignant tumor revealed none. A biopsy specimen from the abdomen was interpreted by Dr. G. F. Machacek as showing epidermal verrucous nevus. He added that the histologic characteristics of the section could conceivably be compatible with acanthosis nigricans, but that pigment was scarce in the basal layer and areas of thinning of the epidermis were not apparent.

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19. Wise, F.: Acanthosis Nigricans, Arch. Dermat. & Syph. **41**:797 (April) 1940.

20. Curth, H. O.: Acanthosis Nigricans, "Benign" Type, presented before the meeting of the New York Academy of Medicine, Section of Dermatology and Syphilis, April, 1948.

Comment: The dermatosis was present at birth in two of the five patients (Cases 12 and 15) and appeared in two (Cases 11 and 13) in the first years of life. Three patients (Cases 11, 12, and 13) continued to show increasing involvement during childhood; the eruption of one (Case 15) has regressed rather than progressed. The dermatoses of two patients (Cases 11 and 13) were at their height at puberty. The regression after adolescence in one (Case 13) has been remarkable.

Fig. 2 (Case 14).—Right axilla, trunk, and neck of a 41-year-old man, showing pronounced changes of "benign" acanthosis nigricans with a considerable number of moles.

Large areas have completely cleared in a short time; lately, however, lesions have reappeared on the abdomen at sites of pressure from a belt. One patient (Case 14) showed the first signs of acanthosis nigricans at puberty, and the dermatosis became almost generalized; from his early thirties on, however, the patient has noticed some regression.

In every instance search for a malignant tumor has been unsuccessful. This fact and the long periods of freedom from malignant disease observed in some of

the patients add to the conviction that these cases are of the "benign" type. Even more reassuring has been the nonprogressive character of the dermatosis.

Criteria for the "benign" type have been fulfilled also in Case 12. The child was born with cutaneous lesions which have slowly spread. He is likely to be suffering from the "benign" type, but since "malignant" acanthosis nigricans can start in a similar manner, the final diagnosis of the type of dermatosis will have to be deferred.

Examinations for endocrine disturbances undertaken in some of the patients resulted in normal findings.

In Cases 11, 14, and 15 the histologic diagnosis was epidermal nevus or epidermal verrucous nevus rather than acanthosis nigricans. The nevoid character of the dermatosis, obvious in the clinical picture, was evident in the histologic picture also. In previous publications [21] I have pointed out that many cases of epidermal nevi most probably have been those of "benign" acanthosis nigricans. I described a patient (J. B.)[21d] who had at birth a small unilateral epidermal nevus which at puberty increased in size and was accompanied with widespread, symmetric, classic signs of "benign" acanthosis nigricans. When I saw the patient again in his 28th year, the nevus had remained more or less stationary and the symmetric cutaneous changes had disappeared. The fact that in a patient symmetric "benign" acanthosis nigricans has occurred together with a unilateral epidermal nevus, the histologic characteristics of which have been indistinguishable from those of the symmetric lesions, speaks in favor of the identity of certain epidermal nevi with "benign" acanthosis nigricans.

It was observed that even in instances of particularly widespread "benign" acanthosis nigricans (Cases 11 and 14) most mucous membranes have remained free.

Of the group, the fourth patient (Case 14) showed the severest cutaneous changes. In this instance particularly, Samberger's [22] remarks that acanthosiform nevi were reminiscent of the amphibian stage through which the human race had passed, seemed appropriate.

2. Simulation of Acanthosis Nigricans (Pseudo Acanthosis Nigricans).—During my studies it became necessary to distinguish from acanthosis nigricans a dermatosis which, occurring in the body creases of obese, brunette persons, simulates acanthosis nigricans.[22a] I named this dermatosis pseudo acanthosis nigricans.[21g] It is this condition, apparently, which Becker [23] described as follows: "One would find mild acanthosis nigricans more frequently in obese persons, if it was carefully sought for." Pseudo acanthosis nigricans seems to depend on factors accompany-

21. (*a*) Curth.[3] (*b*) Curth.[17] (*c*) Curth.[20] Curth, H. O.: (*d*) Benign Type of Acanthosis Nigricans: Etiology, Arch. Dermat. & Syph. **34**:353-366 (Sept.) 1936; (*e*) The Problem of Acanthosis Nigricans, Zoologica **35**:7-8 (April 17) 1950; (*f*) Acanthosis Nigricans (?), Arch. Dermat. & Syph. **60**:441 (Sept.) 1949; (*g*) Pseudo acanthosis nigricans, Ann. dermat. et syph. **78**:417-429 (July-Aug.), 1951; (*h*) The Problem of Acanthosis Nigricans, read before the Fifth International Cancer Congress, Paris, July, 1950; to be published.

22. Samberger, F.: Die Hautnaevi als Quelle anthropologischer Erkenntnisse, Dermat. Wchnschr. **96**:45-57 (Jan. 14) 1933.

22a. After completion of this paper, I learned that D. Argüelles Casals (Sobre una distrofia papilar y pigmentaria del tipo de la acanthosis nigicans frecuente en la raza negra, Med. latina **8**:249-250 [July-Dec.] 1949) had noted the same cutaneous changes in Negroes.

23. Becker, S. W., in discussion on Senear, F. E., and Cornbleet, T.: A Case for Diagnosis (Acanthosis Nigricans), Arch. Dermat. & Syph. **19**:511-512 (March) 1929.

ing obesity, because it develops when the patient puts on weight and disappears when he loses it. In true acanthosis nigricans, which is seen in obese and nonobese persons, dependence on external factors has not been observed.

The pathologic changes of pseudo acanthosis nigricans are not qualitatively different from those of true acanthosis nigricans, but the histologic changes (Fig. 3), as well as the distribution on the body, are on a smaller scale than in true acanthosis nigricans. Likewise, the mucous membranes are not involved in pseudo acanthosis nigricans; they may or may not be involved in true acanthosis nigricans.

Pseudo acanthosis nigricans is seen only in darkly pigmented persons, while patients suffering from true acanthosis nigricans may be either darkly or lightly

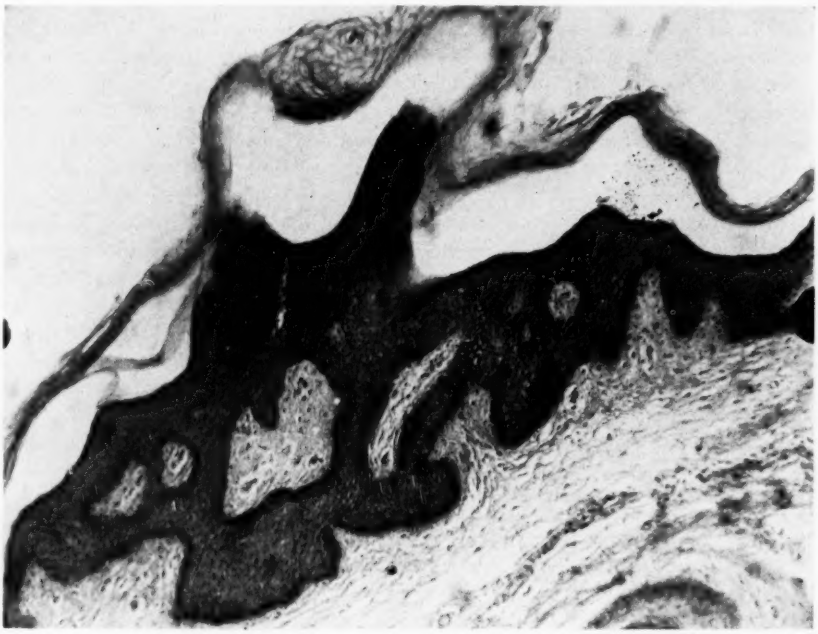

Fig. 3.—Biopsy section from left axilla of a 39-year-old Negro woman, weighing 223 lb. (101 kg.). She had acanthosis-nigricans-like changes in the axillae, on the neck, and on the inner upper aspects of both thighs. Histologic diagnosis of Dr. G. F. Machacek was acanthosis nigricans. In view of the fact that patient is an obese Negro woman, and that the mild cutaneous involvement has remained unchanged for six years, the dermatosis is now considered to be pseudo rather than true acanthosis nigricans.

pigmented. For that reason, the light hair coloring of patients with "malignant" (?) (Case 2) and "benign" (Cases 12 and 13) acanthosis nigricans has been expressly noted.

Some patients reported in the literature as having acanthosis nigricans or referred to me personally as having acanthosis nigricans have had pseudo acanthosis nigricans. Since children at prepuberty often gain weight and display accompanying acanthosis-nigricans-like changes, incorrectly classified cases of this kind have been considered instances of "benign" acanthosis nigricans. On the other hand, when

malignant tumors were present some observers mistook minimal deviations in the axillae and other creases of obese persons for "malignant" acanthosis nigricans.

Differentiation between true and pseudo acanthosis nigricans is necessary for several reasons. First, the needless anxiety of believing they are suffering from a disease which is in some way related to cancer can be lifted from patients who have pseudo acanthosis nigricans. Second, patients with pseudo acanthosis nigricans can be treated rationally, since the cutaneous changes disappear with reduction of weight. The third reason is theoretical: It is pseudo, not true, acanthosis nigricans which is dependent on obesity considered to be an endocrine disorder. Therefore, theories promulgating true acanthosis nigricans as due to an endocrine disorder, because of its association with obesity, are not valid.

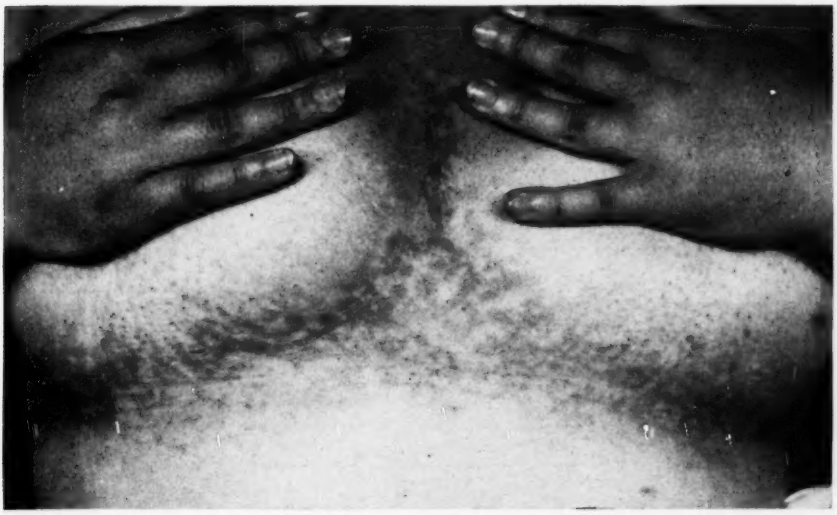

Fig. 4.—Intermammary changes of pseudo acanthosis nigricans, resembling those described as *papillomatose confluente et réticulée* by Gougerot and Carteaud.[24] The patient was a 14-year-old, very obese girl (Andrews, G. C.: Papillomatosis of Gougerot and Carteaud; Case, presented before the meeting of the Manhattan Dermatologic Society, New York, Jan. 9, 1951), showing acanthosis-nigricans-like changes on anterior aspect of axillae, back of neck, and between breasts. Three months later she had lost considerable weight, and the cutaneous changes had subsided.

Patients suffering from pseudo acanthosis nigricans may at times show changes below the breasts and in the intermammary areas (Fig. 4)) similar to those described as *papillomatose confluente et réticulée* by Gougerot and Carteaud.[24]

If one is dealing with slight, pigmented, verrucous changes of the body folds in stout persons, only prolonged observation will settle the diagnostic question of true or pseudo acanthosis nigricans, since true acanthosis nigricans occasionally occurs in obese persons.

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24. Gougerot, H., and Carteaud, A.: Neue Formen der Papillomatose, Arch. Dermat. u. Syph. **165**:232-267, 1932; Acanthosis Nigricans, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, Vol. 6, pp. 416-428.

3. Studies on Progression and Regression of the Dermatosis.—Scars in patients suffering from acanthosis nigricans are good study objects for determining the phase of the disease. Their clinical appearance varies according to whether the wounds which have led to the scars were contracted during progressive or regressive stages of the dermatosis.

The following observations on scars were made:

A. Progressive Stage: In L. B. (Case 2), two years after an operation on the left rudimentary kidney for possible cancer, hypertrophic pigmented changes surrounded the scar.[24a]

B. Regressive Stage: In 1948, when L. H. (Case 13) was 14 years old, a biopsy was performed on the right side of the abdomen, which at that time was covered with lesions of acanthosis nigricans. In 1950, the smooth scar resulting from the biopsy lay in the middle of normal skin.

Comment: The observations on Case 2 show that during progressive phases of the dermatosis a wound leading to scarring provokes new lesions which surround the borders of the scar. The scar itself can obviously not produce the complicated

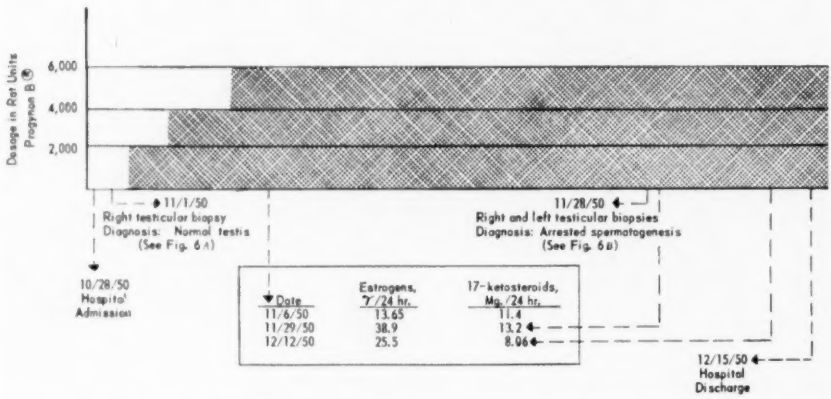

Fig. 5 (Case 11).—Chart showing dosage of progynon-B® (estradiol benzoate), the results of assays of urinary estrogens and 17-ketosteroids, and dates of testicular biopsies.

epithelial changes of acanthosis nigricans. The patient's latest scar should also be watched for new lesions. The arrangement of pigmentary changes during progressive phases of acanthosis nigricans is in contrast to that in Addison's disease, in which the scar itself takes on a dark shade while the borders remain unchanged. The second patient (Case 13) with a smooth scar situated in a formerly involved area illustrates that during the regressive stage of the dermatosis a scar remains unchanged.

In Case 13 regression of lesions took place rapidly in various areas.[24b]

4. Treatment of the Dermatosis by Inducing Hormonal Imbalance.—If the activating influence of a factor connected with puberty on "benign" acanthosis

24a. No report on the behavior of the latest operative scar has as yet been received.

24b. T. Cochrane and J. O'D. Alexander (Acanthosis Nigricans, Brit. J. Dermat. **63**:225-230 [June] 1951) noted after massive doses of vitamin A considerable improvement of the cutaneous hyperkeratosis, but not of the pigmentation, in a patient suffering from "malignant" acanthosis nigricans and adenocarcinoma of the esophagus.

nigricans were proved, rational treatment of this type would consist in reducing or eliminating this particular factor. I have pointed out that the lesions of the "benign" type become worse at puberty and that they may subside after adolescence. I may add that there is a significantly high incidence of "benign" acanthosis nigricans at adolescence. Other evidence of the activation of "benign" acanthosis nigricans at puberty is afforded by the data on the onset of the dermatosis in a family described by Jadassohn.[25] The mother and one daughter showed the first signs of "benign" acanthosis nigricans at the time of their first menstruations. A daughter 10 years of age, not yet menstruating, was free from lesions, but the dermatosis had recently appeared in an 11-year-old son.

Evidence that removal of testes cures "benign" acanthosis nigricans was obtained by chance. In a man who was a habitual sex offender, Hellerström[26] observed that "benign" acanthosis nigricans and, incidentally, accompanying diabetes, had disappeared after castration.

This procedure was not feasible in my patients. However, I repeated with some modifications the experiments of Heckel and Steinmetz,[27] who showed that temporary castration in males could be produced by administration of female sex hormones.

In Presbyterian Hospital, New York, one patient (Case 11), a 28-year-old man, was given large doses of estradiol benzoate (progynon-B®)[28] daily in order to create hormonal imbalance. The dosage and the results of testicular biopsies and assays of urinary estrogens and 17-ketosteroids are reproduced in Figure 5. The skin of the patient was examined daily. Biopsy specimens of lesions before and after treatment were not taken because they were not considered good indicators of slight histologic changes.

Comment: It was noted that the skin actually did get lighter and softer. This result from estrogen therapy could not be predicted. Instead of a tendency to neutralize the effect of the male hormones, the female hormones might have increased the existing pigmentation of this man, since they may be the inciters of "benign" acanthosis nigricans in females.

Biopsy specimens examined by Dr. M. M. Melicow disclosed noteworthy testicular changes (Fig. 6) brought about by treatment with estrogens.

At the end of the experiment, the 17-ketosteroids showed a somewhat depressed value and the estrogens rose to about twice or three times the values obtained at the beginning of the experiment.

Tablets of ethinyl estradiol, 1 mg. daily, were given for oral administration at home. After several weeks the treatment had to be discontinued, since attacks of petit mal such as had been observed in the patient's childhood recurred. After discontinuance of treatment, the attacks stopped and the cutaneous changes assumed their old proportions.

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25. Jadassohn, W.: Familiäre Acanthosis nigricans, kombiniert mit Stoffwechselstörung (pathologische Fettsucht), Zentralbl. Haut- und Geschlechtskr. **21**:43, 1927.

26. Hellerström, S.: Zur Kenntnis der Acanthosis nigricans: Weitgehende Rückbildung der Hauterscheinungen nach Kastration, Acta dermat.-venereol. **14**:86-98 (June) 1933.

27. Heckel, N. J., and Steinmetz, C. R.: The Effect of Female Sex Hormone on the Function of the Human Testis, J. Urol. **46**:319-321 (Aug.) 1941; Production of Azoospermia in Men from the Use of Alpha-Estradiol Benzoate (Progynon-B), Proc. Soc. Exper. Biol. & Med. **46**:174-176 (Jan.) 1941.

28. Estradiol benzoate was supplied by The Schering Corporation, Bloomfield, N. J.

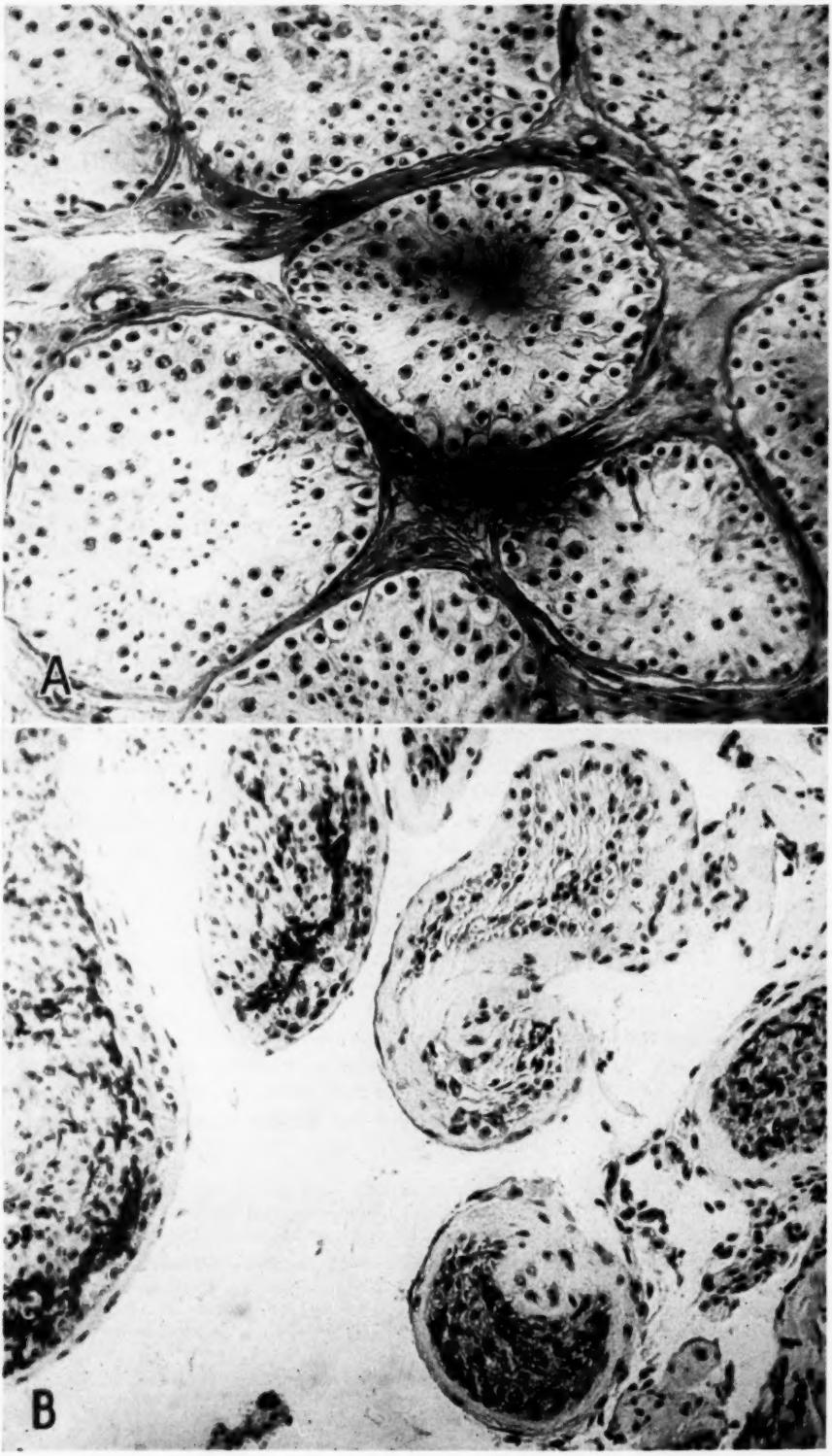

Figure 6

(See legend on opposite page)

It is planned to subject dogs with acanthosis nigricans to hormonal imbalance. This form of therapy, however, has not been contemplated for children suffering from the dermatosis because of the possible interference with normal development. Treatment with the adrenal cortex hormones and corticotropin has recently been instituted. No response to the treatment was seen in benign acanthosis nigricans in Case 15, which will be reported elsewhere.[29]

5. *Inherited Malformations or Disorders Associated with Acanthosis Nigricans.*—Many inherited anomalies of various types were noted in my patients with "benign" acanthosis nigricans. Von Recklinghausen's disease (neurofibromatosis) and mental retardation were seen in Case 15, and a degenerative disorder of the spinal cord involving the pyramidal tracts was present in Case 12. In Case 11 epilepsy and mental retardation existed, a complication often encountered in another genodermatosis, adenoma sebaceum. Various kinds of inherited disorders associated with "benign" acanthosis nigricans have been reported in the literature. Those occurring in association with "benign" acanthosis nigricans in several family members were chondrodystrophy,[30] dwarfism,[31] and mental retardation in association with diabetes mellitus.[32] The presence of a significant number of inherited disturbances in patients suffering from the dermatosis would support the belief that acanthosis nigricans is a genodermatosis. It is, therefore, of interest to find out if a significant number of inherited disorders exists in patients with the "malignant" type of the disease, the genodermatotic character of which has not yet been proved. Among my patients with "malignant" acanthosis nigricans, only one (Case 2) had congenital anomalies. She was born with a rudimentary kidney and ureter and had a supernumerary nipple. There are in the families of patients with "benign" and "malignant" acanthosis nigricans many relatives with various malformations.

29. Hopkins, J. G.; Kesten, B. M.; Nelson, C. T.; Hambrick, G. W., Jr.; Jennings, R. G., Jr., and Machacek, G. F.: Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Diseases of the Skin: II. Allergic and Other Dermatoses; Report of 67 Cases, A. M. A. Arch. Dermat. & Syph. **65**:401-421 (April) 1952.

30. Lange-Cosack, H.: Chondrodystrophie und Acanthosis nigricans: Zur Frage der Persönlichkeit der Chondrodystrophiker und der Gradausprägung chondrodystrophischer Merkmale, Ztschr. menschl. Vererb.- u. Konstitutionslehre **23**:94-112, 1939.

31. Kemeri, D.: Benign Juvenile Acanthosis Nigricans and Hypothyroidism in 5 Members of Family, Orvosi hetil. **81**:329-331 (March 27) 1937; abstracted, Zentralbl. Haut- u. Geschlechtskr. **56**:460, 1937.

32. Hellerström.[26] Bloch, B.: Familiäre Form der juvenilen Acanthosis nigricans, kombiniert mit Diabetes, Schweiz. med. Wchnschr. **50**:414, 1920. Miescher, G.: Zwei Fälle von congenitaler familiärer Akanthosis nigricans kombiniert mit Diabetes mellitus, Dermat. Ztschr. **32**:276-305, 1921.

EXPLANATION OF FIGURE 6

(Case 11).—*A*, testicular biopsy was performed before institution of estrogen therapy. Section of normal right testis shows normal germinal epithelium and complete spermatogenesis through the stage of spermatids. Interstitial cells are in evidence but are not increased. *B*, testicular biopsy specimen taken during estrogen therapy. Right testis shows disturbed and arrested spermatogenesis and thickening of tubular walls. Section reveals definite change from previous biopsy specimen (Fig., *A*). Tubular walls are thickened, and spermatogenesis is disrupted and in some tubules absent. Lumens are occluded by cellular masses and debris. Some of the tubules show a relative increase in Sertoli cells. Interstitial cells are not increased and appear elongated, resembling fibroblasts.

A relative of one patient (Case 9) was a "monster covered with brown spots and having a tail." Other members of this family and of that of another patient (Case 10) had various congenital malformations. Many members of other families had supernumerary nipples. It will take further observations to see whether inherited disorders occurred in a significant number in relatives of patients with the dermatosis, and, if they occurred, whether there was a difference between families with "benign" and those with "malignant" acanthosis nigricans.

SUMMARY

Acanthosis nigricans, a benign dermatosis, represents a unique phenomenon so far as it occurs in two different types which permit comparative analysis of many aspects of the problem. The "malignant" type, which in 100% of cases is associated with internal adenocarcinoma, and the "benign" type, with no such association, present many problems significant in cancer research.

Fifteen cases of the disease, of which 11 are reported for the first time, are analyzed. Criteria for the two types are given. It is possible to recognize the "malignant" type pending manifestation of cancer in those instances in which the cutaneous disorder precedes any signs of cancer.

Rational treatment of the dermatosis is suggested.

Pseudo acanthosis nigricans, a dermatosis simulating true acanthosis nigricans, is described.

35 E. 84th St. (28).

EXFOLIATIVE DERMATITIS DUE TO BANTHINE®

ROBERT F. CLARK, M.D.
AND
DONALD W. McNAUGHTON, M.D.
SEATTLE

BANTHINE® (β-diethylaminoethyl xanthene-9-carboxylate methobromide) has been used successfully in the treatment of peptic ulcer for at least two years. During this time, very few toxic symptoms have been reported. As fas as we have been able to determine, there has been no report of dermatitis due to the drug.[1]

REPORT OF A CASE

J. H., a 60-year-old white man, was admitted to the Seattle Marine Hospital on July 7, 1950. On admission, the patient presented the usual signs and symptoms of congestive heart failure. He complained of shortness of breath of two years' duration and dependent edema which had persisted for approximately one year prior to his present admission.

The past history indicated that he had had the usual childhood illnesses. Adult illnesses consisted of cardiac decompensation and hypertensive vascular disease which had been treated by several physicians in the past. He gave no past history of dermatitis. In 1938 the patient had been treated for a duodenal ulcer on a medical regimen with complete relief of symptoms. The patient stated that he had been in excellent health until 1948, at which time dyspnea and dependent edema of the ankles developed making it impossible for him to work.

Routine physical examination on admission to the hospital revealed a blood pressure of 160/100 and a pulse rate of 100. Eyes, ears, nose, and throat were normal except for arteriosclerotic changes visible on fundus examination and a slight postnasal discharge. Chest examination revealed increased anteroposterior diameter. Rales were heard posteriorly over both lung fields, particularly in the bases. The heart was enlarged to the left on percussion, and no

From the U. S. Marine Hospital.

1. Longino, F. H.; Grimson, K. S.; Chittum, J. R., and Metcalf, B. H.: An Orally Effective Quaternary Amine, Banthine, Capable of Reducing Gastric Motility and Secretions, Gastroenterology **14**:301 (Feb.) 1950. Grimson, K. S.: A Clinical Trial of Banthine in Cases of Peptic Ulcer, ibid. **14**:583 (April) 1950; Cholinergic and Anticholinergic Drugs and Their Trial in Treatment of Gastrointestinal Disorders: Trial of Urecholine and Banthine, New York J. Med. **50**:2028 (Sept. 1) 1950. Walters, R. L.; Morgan, J. A., and Beal, J. M.: Effects of β-Diethylaminoethyl Xanthene-9-Carboxylate Methobromide (Banthine) on Human Gastrointestinal Function, Proc. Soc. Exper. Biol. & Med. **74**:526 (July) 1950. Hambouger, W. E.; Cook, D. L.; Winbury, M. M., and Freese, H. B.: Pharmacology of β-Diethylaminoethyl Xanthene-9-Carboxylate Methobromide (Banthine) and Chloride, J. Pharmacol. & Exper. Therap. **99**:245 (June) 1950. Winkelstein, A.: Banthine® in the Therapy of Peptic Ulcer, J. A. M. A. **144**:1501 (Dec. 23) 1950. Grimson, K. S.; Lyons, C. K.; Watkins, W. T., and Callaway, J. L.: Successful Treatment of Hyperhydrosis with Banthine,® ibid. **143**:1331 (Aug. 12) 1950. Grimson, K. S.; Lyons, C. K., and Reeves, R. J.: Clinical Trial of Banthine in Peptic Ulcer, ibid. **143**:873 (July 8) 1950. Smith, C. A.; Woodward, E. R.; Janes, C. W., and Dragstedt, L. R.: The Effect of Banthine on Gastric Secretion in Man and Experimental Animals, Gastroenterology **15**:718 (Aug.) 1950. Benjamine, F. B.; Rosiere, C. E., and Grossman, M. I.: A Comparison of the Effectiveness of Banthine and Atropine in Depressing Gastric Acid Secretion in Man and the Dog, ibid. **15**:727 (Aug.) 1950.

murmurs were heard. The abdomen was obese, with shifting dullness at the flanks. The liver was enlarged and tender to palpation.

Laboratory studies on admission revealed a white cell count of 17,000 and a sedimentation rate of 10 mm. in one hour. The urine gave a 2+ reaction for albumin and contained many hyaline granular casts. The blood urea nitrogen was 71 mg. per 100 cc. The vital capacity was 63% of normal. The hemoglobin content was 12.7 gm. The red blood cell count was 4,230,000. An electrocardiogram taken on admission revealed myocardial disease with multiple ventricular ectopic beats and left ventricular strain. A chest roentgenogram revealed passive congestion associated with low-grade pneumonia in the lower right part of the lung.

During the course of his hospitalization, the patient received the usual medications and therapy for his congestive failure, which included aminophylline, meralluride ("mercuhydrin"), ammonium chloride, digitalis, phenobarbital, papaverine, morphine sulfate, and atropine sulfate. He responded fairly well to this treatment. At the end of one month, he noted the gradual onset of an epigastric pain which radiated to the back. Abdominal examination at that time revealed tenderness in the lower abdomen. A gastrointestinal series revealed a large duodenal ulcer. At this time, the stool was positive for occult blood. Shortly after the gastrointestinal series was made, the patient experienced gastric hemorrhage on several occasions, and blood transfusions were administered periodically. The usual ulcer regimen including a bland, salt-free diet, tincture of belladonna, aluminum hydroxide gel (amphojel®)and banthine,® was prescribed. The banthine® was given on Nov. 24, 1950, 100 mg. every six hours for two days followed by 50 mg. every six hours. The patient received the banthine® for a total of 11 days. He was noted to have a papular erythema over a large part of his body on Dec. 1, 1950, eight days after the beginning of banthine® therapy. This rapidly developed into an acute generalized exfoliative dermatitis. It was also noted that administration of meralluride was discontinued prior to the onset of the dermatitis. The patient stated that the pruritus became less immediately after use of banthine® was discontinued, and improvement in the skin was noted to some degree shortly thereafter. When the drug was again given, the dermatitis immediately became worse; hence its use was discontinued permanently.

During the episode of dermatitis, the patient lost his hair, eyebrows, eyelashes, and beard, going through several episodes of complete exfoliation. Skin therapy consisted of applications of bland ointments and compresses as required. He was given crude liver, sodium thiosulfate intravenously, tripelennamine (pyribenzamine®) and daily oatmeal baths. When the exfoliative dermatitis had subsided sufficiently to allow it, the patient was given patch tests with crushed banthine® tablets. At 24 hours, a vesicular positive patch test reaction was noted. Four control patch tests were made on persons who were taking banthine® and persons who were not. All of these elicited entirely negative reactions. Results of patch test with 5% ammoniated mercury ointment and thimerosal (merthiolate®) were negative.

Improvement of the patient's skin condition was noted immediately on discontinuance of the banthine.® After the clearing of the skin, the patient was again treated for his duodenal ulcer; during the time of treatment he complained of varying degrees of generalized pruritus with minimal exfoliative changes, particularly of the shoulders and back. This pruritus, with minimal skin change, persisted for several weeks.

SUMMARY

A case of exfoliative dermatitis attributed to banthine® is presented. A patch test with banthine® elicited a strongly positive reaction. Results of four control patch tests on persons taking and not taking banthine,® administered by the same method, were all negative. Patch tests with 5% ammoniated mercury ointment and thimerosal were negative. It would seem to be conclusive that the dermatitis improved when use of the drug was discontinued, became worse when its use was resumed, and finally improved after complete withdrawal of the drug. The positive patch test reaction, significant in a case of dermatitis venenata, could not be satisfactorily explained in a case of dermatitis medicamentosa in that the patient had not been treated with any drugs chemically related to banthine.®

MULTIPLE PESTICIDES FOR SCABIES AND PEDICULOSIS

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IMPOVEMENT in therapy of scabies and pediculosis during the last several years has been little heralded. Yet, taking into account the large number of persons disturbed by the mites causing these diseases and the relative incapacitation which results, it is a real advance to effect rapid cure and to eliminate propagating sources of contagion without damaging clothing. Any new product offered to the public as a skin insecticide should equal these achievements and perhaps supersede them. The combined use of several pesticides [1] was evaluated with these yardsticks in mind.

The formula of the combination ("gamergent" ointment) used was as follows:

Constituents	%
Hexachlorohexahydrobenzene	1
9-Aminoacridine hydrochloride	0.2
Acylcolaminoformylmethylpyridinium hydrochloride	1

HEXACHLOROHEXAHYDROBENZENE

The hexachlorocyclohexanes were first synthesized in 1825 by Michael Faraday, who combined benzene with chlorine in the presence of sunlight. Slade [2] states that it was Van der Linden who demonstrated the existence of four isomers of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane. According to Wooldridge,[3] when the pure isomers were first isolated in 1943, it was found that only the gamma isomer was sufficiently toxic to be of value as an insecticide.

The chemotherapeutic activity of hexachlorohexahydrobenzene has been attributed by Kornblee and Combes [4] to its similarity in structure and action to inositol (hexahydroxycyclohexane). These investigators have pointed out that the meso-isomer of inositol is the active factor, the structural similarity warranting the assumption that hexachlorocyclohexane replaces a molecule or blocks its function in the same

From the Departments of Dermatology, University of Illinois College of Medicine and Cook County Hospital, Chicago.

1. The "gamergent" ointment used in this study was supplied by the Research Department, The National Drug Company, Philadelphia.

2. Slade, R. E.: Chem. & Indust. **64**:40 and 314, 1945.

3. Wooldridge, W. E.: J. Invest. Dermat. **10**:363, 1948.

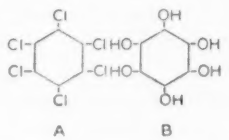
4. Kornblee, L. V., and Combes, F. J.: Arch. Dermat. & Syph. **61**:407, 1950.

manner that paraaminobenzoic acid and the sulfonamides compete. These authors found that the 1% solution of hexachlorohexahydrobenzene was a more effective scabieticide than the 0.5% solution.

In 1948 Wooldridge [3] contended that

> The treatment of scabies has never been entirely satisfactory. Although benzyl benzoate emulsions and ointments have appeared in recent years, none of these newer remedies has entirely supplanted the sulfur-containing ointments. . . . Also, previous methods of therapy have frequently caused chemical dermatitis more difficult to treat and requiring a longer time to cure than the scabies itself. . . .
>
> The gamma isomer of hexachlorocyclohexane . . . has proved to be a remarkably efficient antiscabetic agent in our hands. . . .
>
> Of the 72 patients, 69 were cured with a single twenty-four hour period of treatment. . . . Three patients had relapses and, of these, one was cured with a second course of the ointment. . . .
>
> A distinct advantage of hexachlorocyclohexane was the absence of irritation.

Cannon and McRae [5] found that in 61 of 100 unselected patients with scabies the lesions showed no signs of activity after one treatment with hexachlorocyclohexane; 36 received two treatments, and 3 patients received three. All were cured. A small number of patients with pediculosis were also treated with good results, but were not included in the analysis.



Structural formulas for hexachlorocyclohexane (*A*) and hexahydroxycyclohexane (*B*).

Reporting on the treatment of scabies which had become endemic in a state mental institution, Appel [6] found that an ointment containing the gamma isomer of hexachlorocyclohexane was appreciably more effective than two compounds with similar action, benzyl benzoate and a derivative of crotonotoluide. It was unnecessary to treat for a second time any of the 142 patients who had received the hexachlorohexahydrobenzene.

9-AMINOACRIDINE HYDROCHLORIDE

While the early experimentation with the aminoacridines was largely confined to the treatment of wounds and postsurgical conditions, 9-aminoacridine has recently come to the front as an effective agent in the elimination of parasitic infections, and especially as a scabieticide. As far back as 1943 and 1944 there was in medical literature evidence tending to suggest a desirable synergistic action between hexachlorohexahydrobenzene and 9-aminoacridine as a bactericidal and fungicidal compound.

In 1943 editorials in both the *British Medical Journal* [7] and *The Journal of the American Medical Association* [8] proposed further study and use of the acridine

5. Cannon, A. B., and McRae, M. E.: J. A. M. A. **138**:557, 1948.
6. Appel, B.: New England J. Med. **243**:74, 1950.
7. Editorial, Brit. M. J. **1**:335, 1943.
8. Editorial, J. A. M. A. **122**:117, 1943.

compounds, and a number of investigators [9] reported effective results from use of 9-aminoacridine as a chemotherapeutic agent in wound dressing, the compound being particularly bactericidal against anaerobic organisms.

Ungar and Robinson [10] showed in 1943 and 1944 that 9-aminoacridine (5-aminoacridine in the English system) was a potent antiseptic, satisfactory in high dilutions against Gram-positive cocci and in more concentrated solutions against Gram-positive and Gram-negative bacteria.

Goetchius and Lawrence [11] found that the 9-aminoacridines exhibited bacteriostatic and bactericidal properties similar to those of the most active acridines previously studied. Their antibacterial activity was determined to be largely bactericidal rather than bacteriostatic.

ACYLCOLAMINOFORMYLMETHYLPYRIDINIUM HYDROCHLORIDE

Acylcolaminoformylmethylpyridinium hydrochloride has been used for many years as a cationic detergent antiseptic. Because of its high surface activity it was added to "gamergent" to facilitate penetration of the hexachlorohexahydrobenzene. The therapeutic value of this greater penetration and diffusion seems logical and obvious.

CLINICAL RESULTS

In our series of 41 patients with scabies and 22 patients with pediculosis, the results of treatment seemed to confirm the rationale of "gamergent" ointment and the experience of prior investigators who had reported on each separate constituent.

Scabies.—A total of 41 patients were treated, with known results. Patients were seen daily. Adults used 1 oz. (30 gm.) of "gamergent" for one application on all areas below the clavicles. Children needed smaller, but proportionate amounts. Bed clothes and sleeping clothes were sterilized by boiling, and other clothing was laundered or cleaned. All contacts, especially members of the patients' families, were examined when possible for simultaneous treatment if infested.

These 41 patients were seen again 24 hours after their first examination and after one application of "gamergent." Of these, 40 were judged to be probably free of scabies. Thirty-one returned three days later, and this judgment was confirmed. One patient of the 41, who continued to itch 24 hours after an application of "gamergent," returned the next day after a second application. He then was free of itching. For his first application he had used but ½ oz. (15 gm.) of ointment to cover himself. Several in this group had secondary pyogenic infections. "Gamergent" was applied over the latter sites without untoward effects. Subsequently, appropriate treatment for the pyogenic infections was carried out without incident.

Pediculosis Pubis.—All areas liable to infestation, eyelashes, thighs, abdomen, etc., were scrutinized and treated where affected. Nine men returned a day after the original examination and a liberal application of "gamergent" ointment. Pediculi could be removed easily, which indicated their probable death. Itching ceased in all. Further treatment was withheld. Six patients returned three days later and remained

9. Poate, H. R. G.: Lancet **2**:238, 1944. Bonney, V., and Allen, H. S.: Brit. M. J. **2**:210, 1944.

10. Ungar, J., and Robinson, F. A.: Lancet **2**:285, 1943; J. Pharmacol. & Exper. Therap. **80**:217, 1944.

11. Goetchius, G. R., and Lawrence, C. A.: J. Lab. & Clin. Med. **29**:1177, 1944.

free of itching. Five returned a week later still showing no clinical activity. There were no irritations in this group, although in two patients there was some irritation initially from previously used medicaments.

Pediculosis Capitis.—Seven patients with pediculosis capitis were seen who returned on the following day. About 5 gm. of the ointment was rubbed into the hair carefully and then into the scalp. The hair was covered with wax paper for several hours, and then any excess material was wiped away lightly. No active pediculi could be found on the return of the patients, and nits were loose. Six of the group returned the next day with hair washed and no evidence of pediculosis remaining.

Pediculosis Corporis.—Six men who could be observed three days were in this group. They were sent to a public charity institution for the care of pediculosis corporis. After a bath, 1 oz. of "gamergent" ointment was applied to all parts from the neck downward and sterilized clothes were worn. No evidence of pediculosis could be seen on the third day.

		Pediculosis		
	Scabies	Pubis	Capitis	Corporis
Number of cases	41	9	7	6
24-hour cures (1 application)	40	9	7	6

COMMENT

All the patients found "gamergent" ointment agreeable to use. There was rapid relief, with itching arrested after several hours. None showed any irritation from the medicament. Practically all were well within 24 hours.

CONCLUSION

The combined use of several pesticides, hexachlorohexahydrobenzene, 9-aminoacridine hydrochloride, and acylcolaminoformylmethylpyridinium hydrochloride ("gamergent" ointment), is found to be an agreeable, safe, and rapidly effective cure for scabies and pediculosis.

EXPERIMENTAL EVIDENCE AND CLINICAL STUDIES AS BASIS FOR NOMENCLATURE IN FRAMBESIA TROPICA (YAWS)

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SUCCINCT clarity in nosological nomenclature and standardization of definitions are imperative in all phases of vital statistics and clinical description. Without them, no intelligent comparison of morphological phenomena and epidemiological data is judiciously possible.

The mass campaigns against yaws initiated by the United Nations World Health Organization on an international basis in Haiti, Indonesia, Malaya, the Philippine Islands, and Thailand again call for accurate terminology consistent with ascertained experimental facts and descriptive dermatology. This approach seems to be the only rationale for both sensible and practical nomenclature on which each observer can agree, although he may not see the additional problems in exactly the same way as other experts. The importance of succinct nomenclature as a basis for cooperative international scientific assessments and the magnitude of these yaws control projects are evident from the following figures: In Indonesia alone about 1,500,000 persons in an estimated total population of nearly 2,000,000 will be examined by our teams from June, 1950, to December, 1951, with about 250,000 cases of yaws diagnosed and treated with penicillin in aluminum monostearate.

SUCCINCT NOMENCLATURE IN FRAMBESIOLOGY AND SYPHILOLOGY

Ignorance of established facts in experimental treponematoses, yaws as well as syphilis, is the bane of many writers on merely clinical cases. The cases of yaws seen by the clinician in the dispensary, and by epidemiologists and field workers on surveys, are all in ambulatory patients. They are not cases under strict control. Neither the pathogenesis nor the previous clinical course of the disease is ascertainable beyond reasonable doubt. Only ignorance of the unreliability of human memory, even when remembering is really attempted, could seriously ascribe conclusive value to the patient's volunteered anamnesis. Hence the executant of mere case reports relating to clinical symptomatology is simply unable to give proper emphasis to preceding, as well as to subsequent, morphological characteristics in his yaws patients. Almost invariably, he does not make himself genuinely familiar with all phases of experimental frambesia tropica. The opportunity in the clinic or field to see the very beginning of any type of frambesial change, particularly the earliest, initial skin lesion, is exceedingly rare. To flirt with nomenclature customary in syphilology would mean lack of verisimilitude. In frambesiology, it would mean a

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dead end. Emancipation from such misleading terminology is vital to stop the ever-mounting confusion and misinterpretation. In yaws, as in all realms of medicine, inerrancy of human and animal experiments must be accepted.

EXPERIMENTAL YAWS

The first to undertake experimental research in yaws were Neisser, Baermann, and Halberstädter [1] in Java, Ashburn and Craig [2] in the Philippine Islands, Castellani [3] in Ceylon, and Levaditi and Nattan-Larrier [4] in France. The number of their experiments was small. Their findings were in some instances in agreement, in others inconclusive or even contradictory. Insufficient consideration was given in all instances to adequate controls and the possibility that divergent results or failure in inoculation "takes" were due to the employment of faulty techniques. In 1923 Sellards and Goodpasture,[5] therefore, complained that "the experimental data are extremely meagre," and that "the evidence of tertiary manifestations rests chiefly upon clinical grounds and not upon any exact demonstration in the laboratory." They accordingly commenced studies on experimental yaws in man and in Macacus cynomolgus philippinensis, assisted by Lacy and Schöbl.[6] Large-scale experimental investigations were subsequently continued by Schöbl, Hasselmann, Garcia, and Ramirez [7] at the Bureau of Science and St. Luke's Hospital, Manila, jointly. As the prime result, the definite "epidermotropism" of Treponema pertenue was experimentally established, and the distinct immunological phenomena which both govern and determine the relevant morphological lesions in all stages of yaws were noted.

Extensive inoculations with virulent viable Treponema pallidum and T. pertenue into the Philippine monkey by Schöbl and Hasselmann,[8] and into rabbits by Turner [9]

1. Neisser, A.; Baermann, G., and Halberstädter, L.: Experimentelle Versuche über Framboesia tropica an Affen, München. med. Wchnschr. **53**:1337, 1906. Halberstädter, L.: Weitere Untersuchungen über Framboesia tropica an Affen, Arb. k. Gsndhtsamte. **26**:48-53, 1907.

2. Ashburn, P. M., and Craig, C. F.: Observations upon Treponema Pertenuis (Castellani) of Yaws and the Experimental Production of the Disease in Monkeys, Philippine J. Sc. **2**:441-465, 1907.

3. Castellani, A., cited by Ashburn and Craig.[2]

4. Levaditi, C., and Nattan-Larrier, L.: Contribution à l'étude microbiologique et expérimentale du pian, Ann. I' Inst. Pasteur **22**:260-270, 1908.

5. Sellards, A. W., and Goodpasture, E. W.: Immunity in Yaws, Philippine J. Sc. **22**:233-247, 1923.

6. Goodpasture, E. W.: Histology of Healing Yaws, Philippine J. Sc. **22**:263-281, 1923. Sellards, A. W.; Lacy, G. R., and Schöbl, O.: Superinfection in Yaws, ibid. **30**:463-474, 1926. Schöbl, O.; Sellards, A. W., and Lacy, G. R.: Some Protean Manifestations of Skin Lesions of Yaws, ibid. **30**:475-480, 1926.

7. Schöbl, O.; Hasselmann, C. M.; Garcia, O., and Ramirez, J.: Experimental Yaws in Philippine Monkeys and a Critical Consideration of Our Knowledge Concerning Frambesia Tropica in the Light of Recent Experimental Evidence, Philippine J. Sc. **35**:209-332, 1928.

8. Schöbl, O., and Hasselmann, C. M.: Über Beziehungen zwischen Framboesie und Syphilis, Arch. Schiffs- u. Tropen-Hyg. **36**:1-36, 1932. Hasselmann, C. M.: Framboesie und Syphilis, Zentralbl. Haut- u. Geschlechtskr. **33**:273-299, 1930; Yaws and Syphilis: Problems, Clinical Studies and Experimental Facts Concerning Their Relationship, China M. J. **45**:1131-1155, 1931; Our Present Conception of the Relationship of Yaws to Syphilis, Caduceus, University Hongkong **11**:105-112, 1932; Immunity in Treponematoses, China M. J. **47**:584-586, 1933; Ulcer of the Leg: Its Localization as a Point of Differential Diagnosis in Syphilis and Yaws Endemic Countries, Arch. Dermat. & Syph. **28**:44-52 (July) 1933; Therapy of Treponematoses (Syphilis

resulted in constant and sufficiently different pathological changes, clinical lesions, and clinical course in the respective treponemal infections to prove the distinctness and separateness of the two Treponemata and their clinical entities, viz., syphilis and yaws.

Our observations on experimental yaws in human beings and in animals established that no typical initial yaws lesions need develop at all, and yet typical generalized metastatic polypapillomata could follow. This fact tallies with the frequent experience that the patient is uncertain about the real onset. The generalized stage is only indicative of a previous abortive initial lesion (*frambesia d'emblee*) or perhaps of a "silent infection," a familiar occurrence in all experimental treponematoses. This fact should guard against the frequent latitude in the field in the designation of a certain efflorescence as the "primary" lesion.

INITIAL LESIONS IN YAWS AND IN SYPHILIS

The initial ("primary") lesion in yaws, as in syphilis, is a papule. Already in this stage the different biological behavior of the respective treponemata becomes apparent. T. pertenue of yaws shows marked epidermotropism. The parasites are encountered mainly in the rete Malpighii of the epidermis. Inflammatory response on the part of the host tissues results in hyperkeratosis, parakeratosis, spongiosis, and often enormous acanthosis, with downgrowth of the rete papillae into the cutis and even subcutis, edema of the epidermal cells with vacuolation and degeneration, and disappearance of pigment. Stratum corneum, stratum lucidum, and stratum granulosum may soon be lost. Oozing of serum tends to the formation of a nonadherent, amber-like crust. Extensive leucocytic diapedesis from the underlying corium into the epidermal layers may assume such proportions as to form intraepidermal miliary microabscesses.

The latter reaction emanates from the corium proper. Its strata papillare and reticulare show loose cellular infiltration, but without any sharp outline. The cells are mostly plasma cells, with but a few eosinophiles, round cells, and fibroblasts. Giant cells are rarely seen. By and large, the histopathological characteristics are typical for a plasmocytoma. Here, as well as later on in the generalized metastatic polypapillomatous efflorescences, the blood vessels are not affected. Their intima is intact, without cellular infiltration or endothelial proliferation. No necrosis occurs. Consequently, no ulcer formation is ever present in this early initial stage of frambesia.

The histopathological features of this earliest yaws lesion determine the corresponding morphological changes in the skin. A soft papule, slightly raised above the surface of the skin in the beginning, soon grows in elevation and diameter to a papilloma. There is no induration whatsoever. The tendency to shed the covering

and Yaws) and Quantitative Serum Titration as a Method to Evaluate the Curative Activity of Spirochaeticidal Drugs, Far East Association of Tropical Medicine, Transactions of Ninth Congress, Nanking, 1934; Zur Klinik, Symptomatologie und Loimologie von Framboesie und Syphilis, Ber. phys. med. Gesellsch. Würzburg **61**:51-69, 1937; Syphilis Among Arabs: Bejel and Loath in Iraq and Syria, Firjal and Latta in Palestine, Laghout in Lebanon, Abou-Laghif and Jifár in Trans-Jordan, Arch. Dermat. & Syph. **38**:837-855 (Dec.) 1938; Neuere Ergebnisse der Treponemenforschung: Syphilis, Framboesie und Pinta, Arch. Dermat u. Syph. **189**:104-107, 1949; Unknowns in Yaws, read before the Bangkok International Yaws Symposium, 1952.

9. Turner, T. B.: Studies on the Relationship Between Yaws and Syphilis, Am. J. Hyg. **25**:477-506, 1937.

epidermal surface and to ooze may soon lead to the formation of a nonadherent yellowish crust, consisting of dried serum and epidermal scales. Most important is a total lack of necrosis and ulcer formation at this stage. The French term *framboise* (raspberry) is quite appropriate, if enough contrast exists between the reddish papilloma and the surrounding light-colored skin.

During this early period superinfection is possible in man and in animal if the yaws infection has lasted less than about seven months. After that time immunity may be sufficiently developed that reinoculation will no longer "take."

The duration of the experimental initial yaws lesion at the primary site varies greatly. It may last several months if untreated and may persist during the general-

Fig. 1.—Solitary frambesial papilloma of the breast, presumably "initial lesion."

ized metastatic polypapillomatosis. By local exacerbation it may migrate somewhat per continuitatem to adjacent skin areas. Inasmuch as no period of latency intervenes between this stationary initial local frambesial lesion and the appearance of the locally restricted exacerbation, it is felt that the latter term, rather than *Rezidiv* is appropriate. It should be remembered that in primary syphilis the term *Mono-Rezidiv*, or *solitär-secundär Affect*, explicitly denotes a free interval between the primary chancre and the appearance of a *Rezidiv*.

Partial healing of these late, persisting, initial frambesial lesions, which may have repeatedly exacerbated, has resulted experimentally in even the protean morphological features of lupus-like late nodular yaws lesions.

The not infrequent observation of large skin areas with extensive scarring, sometimes with marked keloid formation, occasionally with resultant contractures

and ankylosis, indicates the diverse healing mechanism of a yaw at this or any later stage of the disease.

On the basis of experimental evidence in man and monkey, it must be assumed that once a patient has gone for a sufficiently long period through typical crops of generalized polypapillomata, his immunity and, therefore, his resistance will be high enough to prevent the appearance, or reappearance, of further frambesial lesions. Permanent reservoirs of T. pertenue in internal organs are not known to exist. Regional lymphatic glands may transitorily harbor virulent, viable T. pertenue only so long as the dependent skin yaw is also rich with them.

The histopathological features and the marked induration of the earliest syphilitic papule are distinct. Acanthosis is of only moderate degree. The superficial

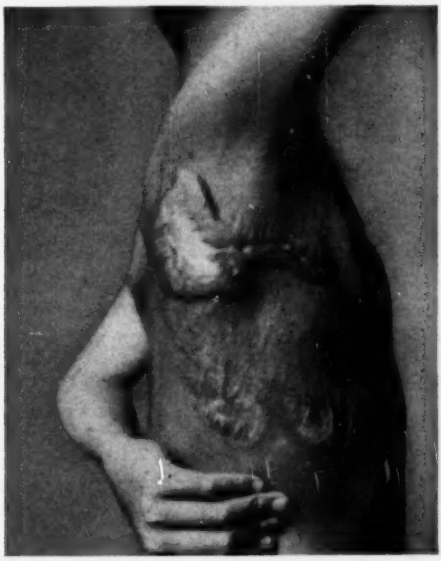

Fig. 2.—Healed frambesial papillomata, with extensive scarring and keloid formation.

epidermal layer is soon lost, and the papules ooze. T. pallidum is encountered in the largest numbers in the mesodermal parts of the skin, i. e., the cutis and the subcutis. Sharply circumscribed infiltrations consist of round cells, fibroblasts, plasma cells, and some eosinophiles and even giant cells. The plasma cells may occasionally show a hyaline degeneration uncommon in frambesia tropica. The capillary blood vessels reveal early cellular infiltration, endothelial proliferation, or even obliteration of lumina.

These pertinent histopathological characteristics of the initial syphilitic lesion account for its clinical aspect and course: The primary indurated syphilitic papule soon progresses into a sharply punched-out ulcer, or chancre. The distinct mesodermotropism of T. pallidum leads to early immunity of such degree that superinfection rarely results in formation of local chancres more than about two weeks after appearance of the primary lesion.

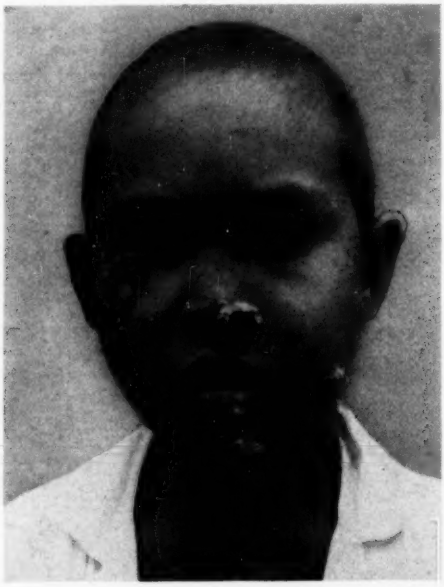

Fig. 3.—Polypapillomata of generalized metastatic stage.

Fig. 4.—Polypapillomata of generalized metastatic stage in two brothers, occurring as a "familial" disease.

GENERALIZED METASTATIC STAGE IN YAWS

Ten to 12 weeks after experimental inoculation of yaws in man and animal, a crop of multiple, generalized, metastatic polypapillomata may appear, usually while the initial yaws lesion is still present. These generalized metastatic frambesial efflorescences also start as papules but soon progress to the typical papillomata. It is highly significant that the histopathological and clinical aspects of these generalized metastatic polypapillomatous lesions are identical with those of the initial frambesial papilloma. This is one profound difference from syphilis, in which the primary chancre and the secondary syphilids are always entirely dissimilar.

The mechanism of appearance of this crop of metastatic polypapillomata is obviously hematogenous. Aside from this, some regional, apparently lymphogenous, propagation of T. pertenue not infrequently leads to rudimentary metastatic papillomata limited to the part of the body on which the initial frambesial lesion is present. They are separated from the initial lesion by stretches of healthy-looking skin. They may be indicative of a tendency inherent in the frambesial process to generalize in successive stages. It was the occasional occurrence of these regional lymphogenous "daughter-yaws" that gave rise to the somewhat ambiguous term "mother-yaw," which now is sometimes loosely used for the persisting initial yaw, if and when generalized metastatic papillomata already coexist.

These early generalized metastatic polypapillomatous frambesids are usually so uniform as to tend to monotony. The medical observer coming from nontropical countries will often be reminded of multiple impetigo lesions, particularly in children. The polypapillomata with their somewhat fungating appearance are easily distinguishable from secondary syphilids, except when the latter also present signs of marked hypertrophy, but then such lesions have long been designated frambesioid syphilids.

If some semicircular arrangement of papules and rudimentary papillomata is evident, the designation ringworm yaws has been used. It is, of course, a peculiar dermatological aspect, not infrequently seen in patients. Usually, other typical multiple papules and papillomata are coexistent, and only some may show this often-overemphasized ringworm-like configuration.

The frambesial efflorescences on palms and soles during this generalized metastatic period deserve special notation. The classical experiments of Schöbl proved that they are "metastatic inflammatory exudative efflorescences," appearing on the palmar and plantar areas simultaneously with crops of typical papillomata on other parts of the integument. Occasionally, they appear in successive crops. Sometimes they are confluent, and map-like exfoliation sets in. The amount of exfoliation and of the occasional subsequent keratosis may vary greatly. Morphologically, it is defensible to use the term psoriasis frambesica palmaris et plantaris, although it would be less misleading to call it frambesiderma psoriasiforme. In this stage, it is indistinguishable from psoriasis palmaris syphilitica, which is more accurately called syphiloderma manus (Fox [10]). As will be pointed out later, these evanescent palmar and plantar frambesids of the generalized metastatic period are not to be confused with the characteristic diffuse hyperkeratotic, often fissured or cribrated, persistent yaws lesion of the late stage known as keratodermia.

10. Fox, H.: Yaws (Frambesia Tropica) as Observed in Haiti, Arch. Dermat. & Syph. **20**:820-834 (Dec.) 1929.

The annular and circinate configuration of papular and papillomatous frambesids, as well as any protean dermatological aspect, may become apparent at any stage of the disease, either evolutional or involutional. The novice must be cognizant of the polymorphous nature of both the course of the disease and its possible skin mani-

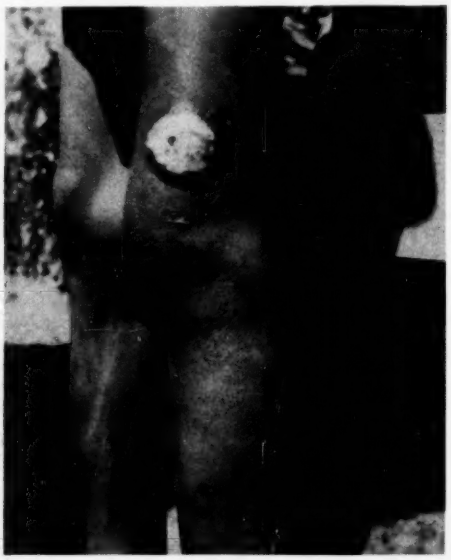

Fig. 5.—Solitary yaws papilloma, presumably "mother-yaw."

Fig. 6.—Solitary yaws papilloma, presumably "mother-yaw."

festations. These depend on the innate tendency of the treponemal infection to exacerbate as long as sufficiently high immunity has not developed. Yet in yaws healing of existing lesions is not necessarily coincidental with resistance to superinfection, i. e., immunity. Either frambesial lesions may heal while the man or animal remains susceptible to superinoculation or they persist long after resistance to superinfection is definitely established, quite in contrast to syphilis. The type of

immunity in yaws is similar, therefore, to that of Bail's "antiaggressive" immunity in symptomatic anthrax (Bacillus sarcophysematos Kitt).

Depending on the degree of immunity reached during the course of the infection, the inflammatory changes and the acanthotic process with formation of typical papillomata may be less pronounced. Frambesids may be present, sometimes coexistent with larger polypapillomata in which conical follicular hyperkeratosis is striking. They represent the dermatological pictures of keratosis pilaris or lichen follicularis, respectively. They may appear on any part of the skin. Usually slight scaling is noticeable, but furfuraceous desquamation is an exception. They are rather atypical, persistent frambesids, appearing somewhat late in the generalized stage. They seem to connote the existence of a partial, though considerable, immunity, inasmuch as attempted superinfection fails in animals.

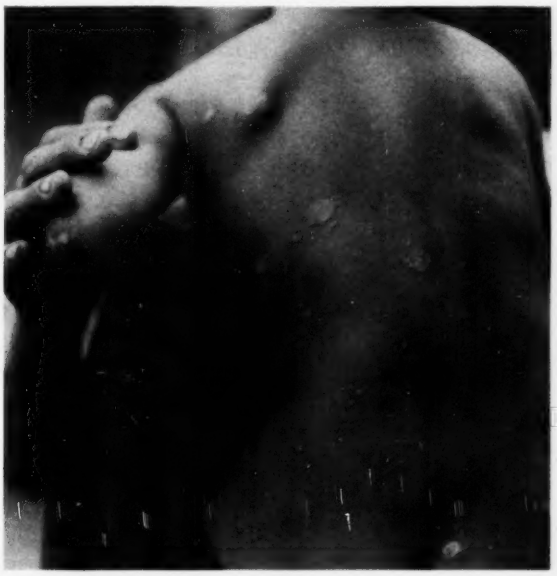

Fig. 7.—Multiple keratosis pilaris lesions appearing as frambesids of later generalized metastatic stage, with coexistent polypapillomata (right buttock) and strongly positive serologic reactions.

Experimentally in monkeys, generalized metastatic polypapillomatous yaws lesions sometimes favored the extensor aspects of wrists, elbows, ankles, knees, and trochanter, though other parts of the integument were also affected.

Papillomata often heal with changes in pigment. Hyperpigmentation is often present and is restricted to the healed yaws lesion. It may persist for a long time. Not infrequently, central hypopigmentation remains as an aftermath of yaws lesions. These depigmented areas at the site of former frambesial efflorescences must be strictly differentiated from leucoderma (Ziemann's *Mbelung* [11]), which represents

11. Ziemann, H.: Ueber Mbelung (Bětă bei den Duala Negern) eine eigenartige Hautkrankheit der Neger in West-Afrika, Arch. Dermat. u. Syph. **74**:163-170, 1905.

the typical dermatological vitiligo and is not necessarily of frambesial origin, though occasionally it is coexistent with late yaws lesions of keratodermia.

This usually extensive leucoderma is situated only over the extensor, seldom over the flexor, aspects of hands and feet, never reaching above the lower thirds of forearms and lower legs. Usually it is bilateral and often shows some symmetry, indicative of a disturbance of the pigment metabolism, perhaps of central nervous system and probably of subthalamic origin. It in no way yields to any specific therapy.

It is a moot question whether ichthyosis is a direct sequela of yaws. Experimentally, Schöbl observed on the tail of one monkey papular lesions with distinct desquamative ichthyosis prior to a final fatal outcome. I am inclined to believe that the frequent extensive ichthyosis seen in the tropical native, especially on the lower legs and forearms, is a symptom of nutritional deficiency. Signs of ariboflavinosis, mainly cheilitis, are very common and often coexistent with ichthyosis in the tropics. Local, as well as generalized, alopecia is often noticed in infected monkeys. It usually commences in the parietal regions. It is most pronounced on the tail and the middle parts of the forearms. The hair is restored after specific treatment. However, alopecia also occurs in noninfected animals when general marasmus of other etiology exists. In man, I have not encountered alopecia which could be attributed to yaws beyond reasonable doubt.

LATE MANIFESTATIONS IN YAWS

Aside from the aforementioned persistence of the initial yaws lesions into the late stage of the disease, there are only two principal late manifestations: ulcerative lesions and keratodermia palmaris et plantaris. These are by far the most frequent yaws lesions to be dealt with in mass campaigns. Either manifestation may appear several months or several years after the initial lesion and with or without coexistent active infective papules and papillomata.

Keratodermia Palmaris et Plantaris (Eczema Tyloticum Frambesicum).—Keratodermia of soles and palms has long been associated with late yaws on purely clinical and serological grounds. Schöbl again was the first to succeed in reproducing it experimentally in Macacus cynomolgus philippinensis. It is a diffuse, callous, often fissured thickening of the palms and/or soles. Exfoliation and deep fissuring may produce various pictures, such as map-like defects, a sieve-like appearance (keratodermia frambesica cribratum), or "moth-eaten feet." The histopathological studies show enormous hyperkeratosis with marked parakeratosis and acanthosis, but little inflammation in the corium. Inasmuch as treponemata have never been demonstrated in these late hyperkeratotic palmar and plantar lesions, it seems permissible to speculate whether the pathological process may constitute some allergic tissue response to yaws infection, and thus is comparable to keratodermia blennorrhagica, for example.

In contrast to the palmar and plantar syphiloderma papulosquamosa, the keratodermia of yaws is usually bilateral and, as a rule, shows a greater tendency to scaling and fissuring, due to the enormous hyperkeratosis. Sometimes, there is a callus-like, ragged thickening of the entire sole; at other times more sharply circumscribed horny plugs extend deep into the partially detached skin. Although usually those parts of the soles are affected which are exposed to constant pressure from weight

and trauma, it is often remarkable that parts of the sole which in no way bear the weight of the body are also affected. From the dorsoplantar and the dorsopalmar borders the changes sometimes spread onto the adjacent dorsal aspects, where the skin then may become ichthyotic and parchment-like.

These late keratodermic yaws manifestations are extremely common wherever yaws occurs. They are very painful to the patient, often incapacitating him for work. The pain on walking leads to a peculiar crab-like gait (hence the term crab yaws). Specific treatment rapidly cures the subjective symptoms of pain. The cornification and serological positivity, however, subside only very slowly.

Considerable confusion has arisen in dermatological and, more specifically, in tropical disease literature from the use of local colloquial names for diseases or their clinical manifestations. Bejel, loath, or firjal for syphilis in the Middle East is one example. Clavos for any hyperkeratotic lesion on soles or palms in Spanish-speaking countries is another. Keratodermia was referred to in the yaws literature emanating from the Spanish Philippine Islands as clavos rather indiscriminately but without

Fig. 8.—Juxta-articular nodules.

prejudice. Stannus [12] once misinterpreted this as clavus, although Gutierrez [13] concisely depicted the opposite morphological characteristics in his pioneer work on yaws in the Philippines. In Spanish, the proper designation for clavus is *ojo de gallo (Hühnerauge)*, whereas the Spanish *clavos* simply denotes any spike-like cornification of the skin.

Ulcerative Lesions: Their Appropriate Terminology.—Deep late ulcerative frambesial lesions never develop metastatically; nor do they arise spontaneously, as in syphilis with its tertiary gummata and tuberocircinate-serpiginous efflorescences. In man as in animal, late ulcerative frambesial lesions develop from preexisting earlier skin lesions of long duration. On the basis of our experimental evidence [6] and my own clinical studies in Manila's St. Luke's Hospital with ample

12. Stannus, H. S.: Trop. Dis. Bull. **24**:300-301, 1927.

13. Gutierrez, P. D.: Keratosis Palmaris et Plantaris Due to Frambesia, Arch. Dermat. & Syph. **8**:382-392 (Sept.) 1923, Fig. 5.

laboratory aid and after seeing tens of thousands of patients in the field, the rationale for the occurrence of ulcerative lesions appears to be as follows: A low-grade yaws infection, either with or without a well-developed initial yaws lesion, causes only a low-grade reactivity in the host. During a negative phase a crop of metastatic papillomata may subsequently appear. These cause a secondary allergic stage, when any sudden increase in antigen may lead to local exacerbation of an existing lesion, be it the initial or a metastatic papillomatous lesion. We have experimentally produced such exacerbations with resulting ulceration. The latter may be confluent. If healing starts from the center, even multiple ulceration is simulated. We are not infrequently confronted with such clinical pictures in the field. It may be repeated that neither in man nor in animal have frambesial ulcerative lesions ever been observed to commence as such, but invariably start from a preexisting yaws lesion, either the initial one or a metastatic yaw.

The existence of a negative phase has been demonstrated both serologically and experimentally. Clinical and experimental evidence strongly suggests an allergic stage at such a phase to allow the obvious local exacerbation with resultant necrosis and ulceration. At whatever stage of the frambesial infection such ulceration sets in, and whether from a preexisting initial papilloma or from generalized metastatic lesions, these late ulcerations do not tell their age or pathogenesis in the ordinary patient.

The customary classification of syphilis into primary, secondary, and tertiary stages succinctly denotes the definite sequence of time and appearance of the syphilids. It also connotes certain definite time intervals, with periods of latency in between. In yaws, no such separation of various stages of the infection exists. It is one of the characteristics of frambesia that all stages overlap. Consequently, the initial yaws lesion a "primary" ulcer, simply because it is factually the initial yaw. Nor would generalization with polypapillomata present, and finally progresses by local exacerbation into an ulcerative process at a late stage. It would be illogical to call the late lesion a "primary" ulcer, himply because it is factually the initial yaw. Nor would it be justified to designate it a "tertiary" lesion on account of its development at this late stage of the infectious disease. Moreover, sometimes generalized metastatic papules and papillomata are still coexistent in that period, which then would have to be called "secondary" by analogy with the nomenclature of syphilology. The paradoxical designation "primary, secondary, tertiary" for such lesions would then apply. Hence, the absurdity of applying nomenclature to frambesiology which is customary in syphilology is obvious.

Furthermore, the relevant histopathological features of the initial yaws lesion and the generalized metastatic papular and papillomatous frambesids are identical, whereas no histopathological similarity exists between the primary syphilitic chancre and the secondary syphilids.

BONE LESIONS

Aside from gangosa, numerous reports have been published on bone lesions in yaws. They have been critically reviewed recently by such an expert as Hackett.[14] No general consensus is discernible on either the types or the pathological characteristics of bone lesions in yaws.

14. Hackett, C. J.: Review of References to Bone Lesions of Yaws, Trop. Dis. Bull. **43**:1091-1104, 1946; Bone Lesions of Yaws in Uganda: A Clinical and Radiological Study, abstracted, ibid. **46**:472-476, 1949.

Experimentally, we have never seen bone lesions develop except by continuity from existing skin lesions. Clinically, one sees bone lesions during the stage of metastatic generalization as well as during the later stages. It has already been pointed out that an allergic condition is probably responsible for their occurrence.

Clinically, the bone lesions without breakdown of tissues, i. e., without ulcer formation, must be differentiated from those in which necrosis of the overlying skin is already present and the underlying osseous tissues are only subsequently involved. The latter are due to allergic exacerbation, as explained before. In the former, thickening and bowing of the tibia (saber tibia), of the forearm, or of the humerus are occasionally seen, especially in children. Since treponemata have never been demonstrated in these lesions, or in the similar syphilitic lesion, it is safe to assume that the bone changes are toxic, perhaps allergic. This view is strengthened by the observations of identical bone changes in children with long-standing pyodermia, etc., as stressed by Chiari.[14a]

Fig. 9.—Large papilloma over abdomen.

Such allergic pathogenesis may apply to conditions like dactylitis of fingers, metatarsals, or metacarpals and involvement of synovia and tendons, sometimes encountered in the field. They subside on specific treatment.

Baermann and Schüffner [15] have described in detail the protean roentgenologic appearance and the subjective complaints of pain in the bones and joints, especially at night. These symptoms may appear as early as the sixth month. The diversity in the reported bone lesions of yaws makes one wonder whether all reports are sufficiently judicious and critical.

14a. von Chiari, O.: Über periostale Knochenveränderungen im frühen Säuglingsalter, Arch. Kinderh. **115**:149-168, 1938.

15. Baermann, G.: Die spezifischen Veränderungen der Haut der Hände und Füsse bei Frambösie, mit einigen allgemeinen Bermerkungen zur Frambösie und ihren Späterscheinungen, Arch. Schiffs- u. Tropen-Hyg. (Supp. 6) **15**:1-23, 1911. Baermann, G., and Schüffner, W.: Die Frambösie-Syphilis-Gruppe, ibid. (Supp. 4) **16**:327-340, 1912.

Some claim that bone lesions are often more generalized in yaws than in syphilis, but that bony atrophy and so-called gummatous osteomyelitis occur more frequently in yaws. The peculiar thickening of the nasal periosteum, with hypertrophy of the spongy tissue (goundou), is probably never found in syphilis. On the other hand, typical osteochondritis is apparently found only in syphilis.

GANGOSA (RHINOPHARYNGITIS MUTILANS)

Ulcerations of the mucocutaneous borders of the nose and mouth and of the palate deserve special attention. They are rather common in yaws patients.

The term gangosa was first used by Ruis de Villalobos in 1828 for patients on Guam with a perforated palate because of their peculiar intonation. Since Leys,[16]

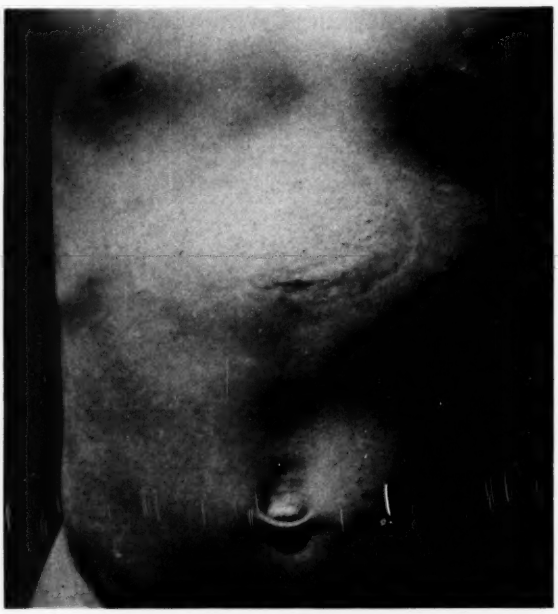

Fig. 10.—Healed large papilloma over abdomen in same patient as in Figure 9 after administration of 1,200,000 units of penicillin in aluminum monostearate (PAM).

the descriptive name rhinopharyngitis mutilans is often used, though he, as well as Mink and McLean,[17] erred by diagnosing as gangosa cases of diphtheria, because "the great majority of these cases prove fatal within 48 hours."

In man and monkey, it is remarkable how initial or generalized metastatic papillomata can linger on the mucocutaneous borders of the nose and mouth. Scars on these junctions are commonly seen among many people. Their location at the corner of the mouth somewhat reminds one of Parrot's scars in syphilis, but, unlike the latter's cicatrization, the frambesial scars are more uniformly flat.

16. Leys, J. F.: Rhino-Pharyngitis Mutilans (Destructive Ulcerous Rhino Pharyngitis): A Problem in Tropical Pathology, J. Trop. Med. **9**:47-51, 1906.

17. Mink, O. J., and McLean, N. T.: Gangosa, J. A. M. A. **47**:1166-1171 (Oct. 13) 1906.

By repeated superinfection, Schöbl and co-workers [7] succeeded in reproducing gangosa of all clinical stages in monkeys:

> Initial or metastatic yaws on mucous membranes are not known to exist; but direct spreading of primary or metastatic yaws from the skin across the mucocutaneous border onto the mucous membrane is by no means an uncommon occurrence. This speaks in favor of my contention that the starting point of gangosa is the skin yaw, either the initial yaw or the late ulcerating yaws lesion, extending directly into the mucous membrane . . . that the [histopathological] process affects a very extensive area of the mucous membrane, far greater than the area which actually undergoes the real ulceration in any stage of the development, and course of the condition . . . by direct extension of skin lesions, either early by [superinfection] or late, onto the mucous membrane of the nose shows that this mode of pathology is the commonest if not the only one.

Clinically and in the field, one can regularly observe cases in all stages of this development. Once an active spreading yaw, whether an initial or a metastatic lesion, is established near the nasal mucosa, only an allergic stage is required to accomplish the destructive mutilation.

It has always struck me that, in contrast to the involvement of the nasal mucosa proper, the papillomatous or condylomatous yaws lesions of the anal region are nearly always perianal, separated from the anal orifice by a narrow strip of healthy-looking skin, unlike the syphilitic condylomata.

The comparatively frequent occurrence of gangosa obviously lies in the close oncogenic relation of the mucous membranes of the facial orifices to the adjacent outer skin. In embryogenesis upgrowth of the mandibular arch and nasal and maxillary processes around the stomodeum forms the final facial contours. For a time, the ectodermal lining comes in contact with the entoderm of the foregut, pressing aside the intervening mesoderm. Hence, in the adult the mucosa up to the pocket of Seessel is closely related to the epidermis. This coincides also with the sensory border of the maxillary trigeminus ramus.

With regard to hereditary disposition, I once found in Sumberedjo, East Java, two boys and one girl with gangosa in one family of six children. In another instance, two sisters in a family of three children were afflicted. Although these are but a few observations, the evidence is baffling.

JUXTA-ARTICULAR NODULES

Juxta-articular nodules are encountered comparatively oftener in yaws than in syphilis. Their histopathological appearance is typical of that of hard fibroma. It is a moot question whether the organisms in these fibroids described as treponemata by van Dijke,[18] Sobernheim [19] and others are not connective tissue fibrils.

THERAPY

Experimentally and clinically, yaws lesions may heal spontaneously, permanently, and without any specific treatment, although this seldom occurs. Positive serological reactions may then be the only indication of the former malady, with or without such sequelae as scars or pigmentary changes. The new antibiotics, especially penicillin, have now replaced the former arsenical and bismuth therapy.

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18. Van Dijke, M. J.; Bakker, C., and Hoesen, H. W.: Contribution to Knowledge of Rhinopharyngitis Mutilans, Meded. Dienst Volksgez. Nederl. Indië **2**:148-171, 1925.

19. Sobernheim, G.: Arch. Schiffs- u. Tropen-Hyg. **28**:73, 1924.

SUMMARY

The present worldwide campaigns against yaws conducted by the United Nations World Health Organization, assisted by the United Nations International Children's Emergency Fund, call for concise and relevant terms to enable logical and unprejudiced description of clinical lesions and their dermatomorphological characteristics.

The striking overlapping of successive stages of frambesial skin efflorescences and their corresponding histopathological features are in singular contrast to the clear-cut divisions into primary, secondary, and tertiary syphilis and to the latter's morphological and pathological diversity.

Executants of mere clinical case reports deal nearly exclusively with ambulatory patients. With neither cognizance of the preceding morphological changes nor an accurate anamnesis, they are prone to enhance the existing confusion in the polyglot literature on yaws, unless they are genuinely familiar with both experimental frambesia and syphilis.

It would be fatuously unreasonable and illogical to refer in frambesia to "primary," "secondary," or "tertiary" lesions and stages as in syphilis, inasmuch as the initial "primary" yaw may persist throughout the entire stage of subsequent generalized metastatic polypapillomata, corresponding to the secondary syphilids, and may suddenly exacerbate into an ulceration at any late stage of the disease, even with polypapillomata coexistent.

In frambesiology, as in all realms of medicine, inerrancy of human and animal experimental investigations must be accepted. Hence it appears sensible and sufficiently descriptive to refer to the lesions as (*a*) initial yaw, whether papular or already papillomatous; (*b*) generalized, metastatic papules and mostly papillomata (polypapillomatous stage); (*c*) the late stage, with (1) keratodermia of soles and/or palms and (2) ulcerative lesions, wherever these are located and irrespective of their indeterminable pathogenesis, except in experimental frambesia.

If further dermatomorphological descriptions of skin efflorescences are considered appropriate for differentiation in a particular patient, such subdivisions and relevant dermatological terms could be used as keratosis-pilaris-like frambesids (*pian d'atre*), which often are coexistent with generalized metastatic polypapillomata; gangosa for the distinct ulcerations of the nose and mouth orifices involving the palate, and ringworm yaws and frambesiderma psoriasiforme to denote the circinate configuration or scaliness, respectively, of any one particular yaws efflorescence.

It is possible by demonstration of viable treponemata to dichotomize between infectious yaws and presumably quiescent or latent clinical lesions. It is not possible to impute that the Treponema-negative, obviously latent frambesial manifestations always remain quiescent; for the course of the disease arbitrarily discloses overlapping of stages; the appearances of crops of efflorescences with even coexistence of different types of clinical lesions, and possible clinical exacerbations of all types of skin efflorescences.

Only the simplest and broadest classification, based on commonly acceptable and logical nomenclature, with uncomplicated reporting, will insure accurate future assessment of the results in the mass campaigns conducted at present in Haiti, Indonesia, Malaya, the Philippine Islands, and Thailand, where often but a few persons adequately trained in dermatology carry the burden of field work.

Clinical Notes, New Instruments and Techniques

POSTACNE SCARS

MILTON S. HARTMAN, M.D.
BROOKLYN

There have been many agents and methods promulgated for the improvement of postacne and other depressed scars. Most have to do with repeated peeling applications of ultraviolet rays, resorcinol, phenol, trichloroacetic acid, salicylic acid, carbon dioxide slush, etc. Many speak glibly of "peeling off" acne scars. This has always seemed extremely implausible to me, since it must be obvious to all that the epidermis regenerates itself, leaving the surface exactly as it was before. Because of the edema produced and consequent temporary lifting of the surface, the scars appear flatter, and the patient reports improvement. However, after the subsidence of the edema, the scars sink to their former level, and nothing has been accomplished.

In order to improve scars, one must produce destruction of the tissue around them and, by so doing, effect an apparent flattening. This is an illusion, of course. The scar is of the same depth as it was before treatment, but is now wider and, therefore, appears flatter. This is acceptable, however, for the patient is now cosmetically improved.

Carbon dioxide slush is very widely used for this purpose. In simple peeling doses it is useless, no matter how often it is applied. It must be administered to the extent that destruction is produced. However, the floor of the scar is included in this destruction and is also rendered deeper. It is, therefore, better to use solid carbon dioxide in order to avoid such contact.

Trichloroacetic acid and phenol, in various dilutions, are also commonly used. Here, again, destruction must be accomplished in order to effect permanent improvement. It is difficult to control these agents; consequently, destruction may proceed to a greater extent than is desired. Entrance into the follicles may result in an unsightly puckered appearance, due to permanent widening of the follicle mouths.

For many year I have used monopolar spark-gap electrodesiccation for "scar removal." Using a small current and various-tipped electrodes (sharp and blunt), the modality is applied to the border of the scar only, gradually covering the entire circumference. There is no more pain than there is in hair removal, perhaps less. The final result is the apparent flattening mentioned above. This method has the obvious disadvantage of being slow and painstaking. However, its advantages are many. It is always under the operator's control, is not applied to uninvolved areas, produces the desired effect, does not traumatize potentially harmful nevi, and does not leave the patient's face covered with large unsightly crusts and bullae after application. An alcoholic, flesh-colored shake lotion is applied afterward, and the patient is given a prescription for the same lotion to be used at liberty between visits. This procedure is especially suited for scars that are deep, that are few, and that are in areas not easily accessible, such as about the nasal furrows and the eyes.

As the dermatologist becomes proficient in this method, he will find that he can accomplish more at one sitting than at first seemed possible. Of course, he must know his machine and carefully test the spark before application, a smooth spark being preferred to a coarse one. I test the spark by rapidly drawing the point across my palm. There is no pain so long as the point is kept moving. Spark-testing by touching a piece of metal on the machine is not accurate because of differences in conductivity. It is not the same spark that is actually applied to the tissues.

In my experience the reverse end of the ordinary pointed electrode usually supplied with the machine has been very suitable as a blunt electrode. This is a great timesaver in changing from the sharp to the blunt point, or vice versa. If the reverse end is not smooth or of the proper convexity, it can be easily filed and polished to the desired shape and smoothness. A slight adjustment of current may be necessary to compensate for the variation in spark concentration, the sharp point producing a more intense spark than the blunt. The spark of the blunt point is more diffuse and therefore of less intensity.

Electrocoagulation, with the patient holding the inactive electrode, may also be used; but here the destruction is deeper and not as easily controlled. Moreover, with electrocoagulation

there is the ever-present possibility of hypertrophic scar formation due to the increased amperage used. This possibility is virtually nonexistent with light electrodesiccation.

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ALOPECIA AND DERMATITIS VENENATA FOLLOWING HAIR STRAIGHTENING

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NEW YORK

I wish to report a case of alopecia and dermatitis venenata following hair straightening, which is similar to the one reported by Anderson.[1]

REPORT OF A CASE

The patient, a married Negro woman aged 32, was referred to me because of loss of hair and irritation of the scalp.

The patient gave a history of having had a hair-straightening treatment at a beauty institute, Oct. 1, 1951. She stated that a hair dressing was placed on her scalp for a half-hour and that this application was followed by combing with a heated heavy metal comb. She remarked that she observed a mild painful stinging reaction of the scalp while receiving the treatment.

The following day, the patient noticed that her hair and scalp felt stiff, and, commencing Oct. 4, the hair began to fall out in patchy areas. She also noted itching of the skin of the front and side of the scalp.

Examination revealed irregular areas of partial alopecia of the parietal and frontal areas of the scalp. The hair was short, stubby, and broken at the ends, and many hairs were matted together. The average hair length of the scalp was ½ in. to 1 in. (1.3 to 2.5 cm.), and the patient mentioned that previously it was 5 to 8 in. (12.7 to 20.3 cm.) in length. There were scaling, erythematous, crusting areas of the skin of the scalp extending along the parietofrontal margins posteriorly to the occipital area.

As previously reported by Anderson, the preparation used in the hair-straightening treatment consists of an alkali, such as sodium hydroxide, dispersed in a wool fat (lanolin)-petrolatum base.

The breaking of the hair, the subsequent alopecia, and the scalp dermatitis are the result of contact with the alkali and heat.

The dermatitis venenata and the progressive loss of scalp hair continued for two months. The hair then began to regrow, and the dermatitis of the scalp cleared completely.

1. Anderson, J. W.: Alopecia from Hair Straightening, Arch. Dermat. & Syph. **62**:910 (Dec.) 1950.

Correspondence

LIVER-FUNCTION TESTS IN STASIS DERMATITIS

To the Editor:—In the February, 1952, issue of the A. M. A. Archives of Dermatology and Syphilology (**65**:236-239), Griffith and Baumeister state that they could find no consistent relationship between the status of the liver and stasis dermatitis. We have reported (Eichenlaub, F. J., and Osbourn, R. A.: Arch. Dermat. & Syph. **57**:171-177 [Feb.] 1948) on a small series of patients who manifested evidence of liver disease in association with stasis dermatitis.

These were patients whose dermatitis had not responded to symptomatic therapy but did become better when we employed measures aimed at improving liver function. In an even smaller series, Griffith and Baumeister rejected our thesis. We do not deny the observations of the latter authors, for we know there are many cases of stasis dermatitis in which the liver function is normal or as near normal as can be determined by present liver-function tests. We did not promulgate a universal law in biology; i. e., we did not claim that all cases of stasis dermatitis are associated with liver disease. We feel that there are many causes for stasis dermatitis and might well point out that not all patients with varicose veins have stasis dermatitis. However, this does not imply that varicose veins are not a causative factor in some cases of stasis dermatitis. Consequently, we felt justified in reporting some cases of stasis dermatitis in which liver damage was present and in which the knowledge of that damage proved to be of clinical value in treating the patient.

If one accepts our thesis, it is not logical to suppose that patients with acute hepatitis would have stasis eczema. Liver disease is not the sole cause, but only a contributory cause acting with other factors. Now, if these other factors are absent, one would not expect liver disease per se to produce the dermatitis.

Such factors, we feel, are age, occupation, degree of ambulation, status of the vascular tree, nutrition, and presence of other diseases. In our patients many of these factors were present. In the hepatitis patients, the liver disease was acute and the age group was younger; they were usually nonambulatory after the liver disease developed, and no doubt the state of the vascular system of the legs in those patients was much better than in our patients. Consequently, we do not expect acute hepatitis to eventuate in stasis eczema. Moreover, one of us (R. A. O.) was also associated with an Army General Hospital and treated almost exclusively for a year a ward full of patients with acute hepatitis. Here, it is true, there were no cases of congestive eczema, but this observer noted that those patients with liver disease who had minor dermatoses of the legs and feet responded much more slowly than similar dermatological patients without liver disease. In fact, this observation and experience with liver disease was one of the things that prompted us to investigate liver functions in stasis dermatitis.

Finally, in studying Griffith and Baumeister's series, we find that four patients (Cases No. 394-264, 353-555, 330-407, and 351-756) show more retention of sulfobromophthalein than was considered normal when we reported on our series (i. e., not more than 5 to 7% retention in the 30-minute specimen and no retention in the 45-minute specimen). If these patients still have their eczema, perhaps measures to improve their liver function will be of value to them.

Raymond A. Osbourn, M.D.,
Washington, D.C.

To the Editor:—We have read with interest Dr. Osbourn's remarks concerning what he feels may be certain differences of opinion in regard to the role of the liver in stasis dermatitis. We are happy that he has come forward with this statement, since the actual differences now appear to be fewer than at the time our article was published.

According to his letter, Dr. Osbourn has studied patients with liver disease who had stasis dermatitis to see whether treatment of the diseased liver would aid in the recovery of the dermatitis. Our purpose was entirely different, i. e. we wished to see whether patients with stasis dermatitis tended to show signs of liver disease. We are in entire agreement that the treatment of any debilitating disease, such as liver disease, in a patient with stasis dermatitis would aid in the recovery of the dermatitis. However, we did not feel that liver disease played any marked etiological role in the majority of cases of stasis dermatitis, a view which is apparently not in conflict with Dr. Osbourn's ideas.

We are left a little in doubt by the final paragraph in Dr. Osbourn's statement, concerning the fact that four of our patients might have liver disease on the basis of the sulfobromophthalein sodium tests and might have their eczema benefited by therapeutic measures directed at the liver. We feel that our standards for this test for a normal liver were really too strict; e. g., Sunderan and Boerner ("Normal Values in Clinical Medicine," Philadelphia, W. B. Saunders Company, 1949) state that retention of less than 10% at the end of 30 minutes and of less than 6% at the end of 45 minutes may be considered normal. Nevertheless, even with our rigid figure of 5 to 8% retention in 30 minutes and no retention in 45 minutes, in Cases 394-264 and 330-407 retention was still within normal limits (5% and 8%). Two other patients (Cases 353-555 and 351-756) had cholecystitis, thereby nullifying the value of the sulfobromophthalein sodium test. In addition, the results of other liver-function tests were normal for these two patients with cholecystitis.

PAUL R. GRIFFITH, M.D., and CARL F. BAUMEISTER, M.D., Berwyn, Ill.

Special Notice

SUPPLEMENTARY ISSUES FOR SOCIETY TRANSACTIONS ONLY

It has been proposed that two supplementary issues of the A. M. A. Archives each year be devoted to Society Transactions only and that the additional cost involved be covered by increasing the subscription price of the journal by $3.00 yearly. Postcard inquiries have been sent to a large sample number of subscribers to learn their reaction to the proposal. Comments of all subscribers concerning this proposal will be welcomed.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Charles R. Rein, M.D., *President*

Henry Silver, M.D., *Secretary*

April 19, 1951

Hemochromatosis. Presented by DR. ALEXANDER A. FISHER, Woodside.

A. A., a man aged 32, was hospitalized for a dropped kidney in 1943 while in the United States Army. In 1945 he was discharged from the Army, and on his arrival home the family noted that there was a change in the color of his skin.

When he was first seen, on Jan. 8, 1951, the entire skin was dusky grayish. The lips appeared cyanotic. The gums and hard palate were a deep purple. The axillary hair was absent, and the hair in the bearded and pubic regions was extremely sparse. The liver was enlarged and quite firm.

The patient complained of moderate weakness and impotence.

On Feb. 15, 1951, he was transferred to the Hospital of Rockefeller Institute for Medical Research for further study.

DISCUSSION

DR. WILLIAM J. EISENMENGER (by invitation): The case presented illustrates the typical early course of a patient with hemochromatosis. The findings of particular significance were the skin pigmentation, the sexual changes, and the cirrhosis of the liver with hepatomegaly. Despite the cirrhosis which was obvious clinically, results of all the liver-function studies were perfectly normal.

The pathogenesis of this disease according to present concepts is briefly as follows: Normally, one ingests approximately 15 mg. of iron a day. Only a minimal amount of this, less than 1 mg. per day, is absorbed from the gastrointestinal tract. This amount balances the endogenous iron lost by the body daily. For an unknown reason, in hemochromatosis the amount of iron absorbed daily is increased tremendously, but the limited ability of the body to lose iron is unchanged. Hence, iron progressively accumulates in the body. At first the excess iron appears to be stored normally as ferritin, this being an iron-protein complex containing approximately 23% iron. As more iron accumulates, there is a further consolidation of the iron-protein complex into hemosiderin, which has an iron content of 35 to 40%. Hemosiderin can be visualized as globules which give a positive reaction for iron on the addition of potassium ferrocyanide. Hemosiderin is demonstrable intracellularly, and in the early stages there is no apparent cellular damage. As the amount of hemosiderin increases, cellular damage and scarring occur.

Symptoms of the disease are determined by the principal sites of iron deposition. Thus, excessive deposition in the liver and pancreas gives rise to the major pathologic changes resulting in cirrhosis and diabetes. While certain of the skin pigmentation may be due to deposition of hemosiderin, giving a bluish color, much of the pigmentation is due to melanin, giving the brown discoloration. Thus, the disease is often called bronze diabetes.

From the above the reason that hemochromatosis is asymptomatic for many years is clear. For, while the disease may be present from birth, it takes many years to accumulate the 25 to 50 gm. of iron which is present when symptoms develop. Also, these factors appear to explain the male sexual preponderance, since the loss of iron through the menses prevents its excessive accumulation in women.

All the iron in serum is bound to a protein, a specific globulin in the $beta_1$ fraction. This protein-bound iron can be determined chemically. Normally, of the total amount of this serum protein which is capable of binding iron, only approximately one-third is actually combined with iron, the remaining two-thirds of this protein being unsaturated.

In hemochromatosis, however, most of the serum-iron-binding protein is saturated with iron. Thus, the serum-protein-bound iron is elevated and the nonsaturated iron-binding protein is reduced in patients with hemochromatosis. Therefore, a positive reaction to the chemical test is practically diagnostic of hemochromatosis. However, because of the implications of such a diagnosis, and in order to be in a better position to evaluate therapy, a hepatic biopsy was done on this patient, and a dense infiltration of hemosiderin throughout the liver was observed. A biopsy specimen obtained from the abdominal skin at the site of the biopsy wound showed only minimal infiltration in the sweat glands. No unusual amount of melanin was seen.

This brings us to the question of treatment. An iron-poor diet can reduce the daily iron intake to approximately 5 mg. per day. Thus, at best this would slow down the process. Therefore, at least in the early stages of therapy, active removal of iron is necessary. The most accessible iron in the body is that in hemoglobin. Accordingly, treatment by multiple phlebotomies has been tried. Beneficial results have been reported by Davis and Arrowsmith, who treated three patients with phlebotomies once or twice a week for more than a year.

The rationale of such treatment is clear from a consideration of the amount of iron in blood. In a pint (473 ml.) of blood there is 250 mg. of iron located almost entirely in the hemoglobin. Hence, weekly phlebotomies effectively reduce the total body iron, and the plasma may be returned to the patient if this is practical. Such frequent phlebotomies cause little, if any, reduction in hemoglobin concentration in such patients because of the ready availability of iron.

DR. ALEXANDER A. FISHER, Woodside: Dr. Eisenmenger has brought us up to date on hemochromatosis and has pointed out a relatively simple treatment which is a ray of hope in this rather hopeless condition.

The patient presented had sparse pubic and axillary hair and had practically no hair in the bearded region. He was also relatively impotent. Would Dr. Eisenmenger explain how the disease brings about the secondary sex changes?

DR. WILLIAM J. EISENMENGER (by invitation): The lack of male hair distribution constitutes one of the earlier signs in most patients with hemochromatosis and apparently reflects again the affinity of iron for glands, including the sexual glands. Sparsity of hair has been present in this patient for many years and for the past two years has become more marked, with the result that while previously he had to shave frequently he now rarely shaves.

DR. WILBERT SACHS: Would determination of the iron content of the sweat be of any value? Dr. Eisenmenger reported that iron was found in the sweat glands as one of the first signs. I should then expect increased sweating, more than normal.

DR. WILLIAM J. EISENMENGER (by invitation): About one year ago there was a report which claimed more loss of iron through the skin than had previously been reported. Previously, all the iron lost from the body daily was considered to be lost through the gastrointestinal tract and to amount to well under 1 mg. In the report referred to, it was claimed that there was a loss of 1 mg. or more through the skin alone daily, but since then, I believe in some studies with radioactive preparations, this has been refuted. The iron is demonstrable in the skin, but that does not mean it was excreted there. I did not intend to imply that the sweat glands constituted one of the first sites for iron deposition. Iron deposition in the skin appears to represent more or less an overflow, and its presence there usually indicates that the liver and pancreas are already heavily saturated with iron.

DR. DAVID B. BALLIN: Is it possible to use some method of removing iron from the gastrointestinal tract, as is being done with sodium?

DR. WILLIAM J. EISENMENGER (by invitation): On a dietary basis the therapeutic aim consists in regulating the acidity and the phosphorus content of the diet. This iron absorption is favored by acidity and ascorbic acid, which promote the conversion from the ferric to the absorbable ferrous state. In the reverse manner, on keeping the intestine alkaline with the presence of excess phosphates, it has been shown that less iron is absorbed because the iron is kept in the ferric state and bound to the phosphate complex. I do not think that thus far anything specific enough against iron has been found.

DR. FRANZ J. HERRMANN: In regard to the physiologic iron elimination through the human skin, the original assumption of Mitchell and Hamilton (*J. Biol. Chem.* **178**:345, 1949) that the iron is excreted in the sweat was subsequently disputed by Adams, Leslie, and Levin (Cor-

respondence, *J. A. M. A.* **143**:391, 1950), who showed that the metal is actually present in shedding scaly materials and not dissolved in the sweat. In this, and in several other respects, the iron's route and distribution closely resemble the fate of other electropositive substances, metals as well as other chemicals. Not unlike the iron, silver is deposited around (not inside) the sweat glands and ducts, chiefly in the myoepithelial elements. Various electropositive chemicals, e. g., quinacrine hydrochloride (atabrine® dihydrochloride), are selectively attracted by the lining of the spiral portion of the sweat ducts but do not necessarily appear in the sweat. For the example of quinacrine, my associates and I found elimination through the skin to be almost exclusively via the sebaceous glands or the shedding horny structures.

Iron salts, like the salts of other heavy metals, are known to tend to complex salt formation in biologic liquids. In these complexes, which form in particular in the presence of major quantities of chlorides (or other halogenides), the iron loses its cationic character and becomes part of an anion. I wonder whether an abnormal reduction of the factors ordinarily producing the anionic transformation could account for excessive formation of iron-protein combinations in the blood plasma, and whether the methods of investigation of Dr. Eisenmenger afford information on the amounts of anionic iron in the plasma.

DR. WILLIAM J. EISENMENGER (by invitation): The serum iron (protein-bound iron) was found by the method of Kitzes, Elvehjem, and Schnette (*J. Biol. Chem.* **155**:653, 1944). The iron-protein complex is a colored substance, while the iron and the iron-binding protein alone have no color. Iron added to serum in vitro combines with the unsaturated iron-binding protein, and the resultant color is measured directly in the Beckman spectrophotometer, according to the method of Roth and Finch (*J. Clin. Invest.* **28**:79, 1949).

DR. WILLIAM LEIFER: I am interested in the interpretation of the feminization of these patients as being due to a direct effect upon the gonadal glands. Why is this not due to the same mechanism as that in cirrhosis of the liver without hemochromatosis? A second question is, what is the reason, or the speculation on the reason, that these persons absorb so much iron? What happens to make them so different?

DR. WILLIAM J. EISENMENGER (by invitation): As far as hypogonadism or feminization of these patients is concerned, this patient has cirrhosis, but at the moment it is cirrhosis as caused by increased scar tissue; with regard to decreased cellular function, results of all the laboratory tests are perfectly normal. Now 10 or more years ago the patient already showed some beginning changes in his secondary sexual characteristics. Thus, secondary sexual characteristics decreased when cirrhotic changes were very early and minor. In the usual case of Laennec's cirrhosis these changes occur only after cirrhotic changes are more advanced. Regarding the second question, one must speculate at present. It appears that there is a balance between ferritin and ferrous iron in the gastrointestinal mucosa and that as iron is carried from the mucosal cells by the serum-protein-iron complex the mucosal iron is reduced, a reduction that somehow stimulates absorption of iron from the gastrointestinal tract, absorption which was formerly blocked. The nature of this mucosal block is inefficient, and a high percentage of ingested iron is absorbed from the mucosal cells despite high levels of serum iron.

DR. EMANUEL MUSKATBLIT: Is there a possibility of introducing any chemical compound into the intestinal tract that would form an insoluble salt and thus prevent absorption of iron, or of introducing such a compound intravenously to turn the insoluble iron deposited in the liver into soluble iron?

DR. WILLIAM J. EISENMENGER (by invitation): With regard to the first question, such a compound would be worth trying, and thus far I do not think anyone has found a practical absorbent. At present one can only speculate regarding the intravenous injection of an agent which would render the ferritin soluble so as to be excreted.

DR. PERRY M. SACHS: Do you find that most of the pigmentation is due to melanin in hemochromatosis?

DR. WILLIAM J. EISENMENGER (by invitation): Pigmentation may be due to melanin, but it is also caused by the adrenal or cortical involvement.

DR. FRANCES PASCHER, Brooklyn: Is there any diminution in the pigment of the skin in patients who do respond to therapy? Has any excess of iron pigment been demonstrated in the skin, as well as in other tissues?

DR. WILLIAM J. EISENMENGER (by invitation): In the only group of patients treated by multiple phlebotomies on whom I have seen a report, no mention was made of any change in pigmentation. I refer to the report in the *Proceedings of the Central Society for Medical Research* for 1950. I do not believe there is any change, but I cannot say definitely.

DR. JULIUS H. POLLOCK: Have isotopes been used as tracers in the study of this disease?

DR. WILLIAM J. EISENMENGER (by invitation): They have been used in measuring the uptake of administered iron.

DR. WILLIAM LEIFER: Can you produce a similar picture in animals by the administration of large amounts of iron? What risk is there in human beings taking iron for long periods by mouth?

DR. WILLIAM J. EISENMENGER (by invitation): You can produce hemochromatosis in animals just as in human beings by numerous transfusions, say 100 to 150 transfusions. An approximate though not entirely similar picture can be produced. The result is a great load of iron in the liver, and the patient may get diabetes, etc. In regard to the prolonged oral administration, the normal mechanism of a mucosal block protects patients from excessive absorption. If a patient does not have enough iron, then the mucosal barrier permits only as much iron to be absorbed as is needed, and the remainder is lost in the stool.

DR. FRANZ J. HERRMANN: With reference to the question by Dr. Muskatblit on which substances might be considered for systemic administration in order to increase the excretion of excessive iron from the body, I should like to remind you of the fact demonstrated by K. Spiro and his school that heavy metals, such as lead and bismuth, are excreted in significantly increased quantity after administration of iodides. The metals then appear in the urine in complex combination with the iodides.

DR. HARRY B. FEILER: Has blood removed from these patients ever been utilized?

DR. WILLIAM J. EISENMENGER (by invitation): It probably has, but I do not think anyone would be happy about using it, because no one knows quite what might result.

DR. WILBERT SACHS: In some cases sections of the skin show a picture just as abnormal as that of the liver. I have never seen iron in the epidermis, either in epithelial cells or in the horny layers; most of it is in the cutis.

DR. WILLIAM J. EISENMENGER (by invitation): In most extreme cases the iron is seen in the heart muscle and in almost every tissue. That occurs in the terminal stages, but in the earlier cases there is little iron outside of the liver and spleen.

Amyloidosis Cutis, Extensive. Presented by DR. DAVID BLOOM.

M. V., a woman aged 64, a patient at the Skin and Cancer Unit of the New York University Hospital-Bellevue Medical Center, presents a generalized eruption of eight years' duration associated with considerable itching. It appeared first on the arms and four years later on the legs. The patient has been suffering for many years from rheumatic pains in the legs and shoulders. The pain in the shoulders was at times so severe that she could not lift her arms.

The eruption involves the anterior aspects of the arms, forearms, upper part of the back, thighs, and upper third of the legs. In these areas there is diffuse hyperpigmentation consisting of closely set spots the size of a pinpoint or pinhead, some arranged in streaks. On the forearms the skin appears lichenified, and on the legs the individual pigmented spots are somewhat elevated.

The serologic tests for syphilis gave negative reactions.

The histological examination of a specimen of the affected skin was reported as revealing amyloidosis cutis.

DISCUSSION

DR. MAX JESSNER: The lesions in this case are mostly macular. This is an extremely rare feature.

DR. ELLEN REINER: In two cases of macular amyloidosis recently presented at the Mount Sinai Hospital, the diagnosis was confirmed by biopsy. The clinical picture simulated that of mild ichthyosis with hyperpigmentation. Both patients complained of pruritus. Both were middle-aged Puerto Rican women.

DR. HANS H. BIBERSTEIN: The macular types described in the literature show greater involvement of the skin than the papular variety.

DR. JOHN GARB: I suggest that vitamin A studies be made, in view of the report by Kittredge (ARCH. DERMAT. & SYPH. **52**:49 [July] 1945) and Peck (ARCH. DERMAT. & SYPH. **62**:348 [Aug.] 1950) in which lack of vitamin A was demonstrated. With regard to the type of lesion, may I point to the case presented by Wise (ARCH. DERMAT. & SYPH. **59**:354 [March] 1949) in which there were diffuse macular lesions on the chest, forearms, and legs? Should the patient fail to respond to vitamin A, podophyllin in an ointment base should be tried (ARCH. DERMAT. & SYPH. **62**:698-702 [Nov.] 1950).

DR. WILBERT SACHS: The diagnosis of amyloidosis did not suggest itself to me. Patients with amyloidosis may have xanthelasma. I have never seen amyloidosis of the eyelids.

DR. DAVID BLOOM: Clinically, a provisional diagnosis of poikiloderma atrophicans vasculare was made, although no telangiectasia and little atrophy was seen. Even the slide stained with hematoxylin and eosin showed hardly any abnormal changes. However, on the careful examination Dr. Kallman detected some alteration in the papillary layer which led to the discovery of amyloid by methylrosaniline chloride (methyl violet) stain.

Generalized Bullous Dyskeratosis Associated with Psoriasis. Presented by DR. FREDERICK REISS.

V. M., a man aged 48, presents a pruritic eruption characterized by abrasions and detachments of the epidermis after mild trauma. There is no family history of any cutaneous disease. The past history is of no diagnostic importance. The first lesions appeared on the forehead and neck about 15 years ago and have since spread to the chest, arms, and face.

When the patient was first examined in August, 1942, there were a widespread exfoliation and a scattered bullous eruption. The entire skin, except the scalp and palms, was involved. Numerous biochemical studies have been made, among the most outstanding findings in which were a depletion of vitamin C and the presence of dehydroascorbic acid. Histological studies showed an irregular epidermis which was thrown into small, wavy interpapillary pegs, covered by a thickened stratum corneum. There was a cleavage of the epidermis which separated the horny layer and, at times, the granular layer from the underlying prickle-cell layer, with the formation of typical lacunar spaces. These spaces were filled with coagulated serum. In certain parts of the section a distinct hyperkeratosis was present, not confined to the follicles. The conspicuous feature of the section was a number of disrupted and partly degenerated prickle cells showing basophilic staining and double contours, characteristic of "corps ronds." The underlying corium was rather dense, with a perivascular lymphocytic infiltration. Elastic tissue stain showed an abundance of coarse and fragmented elastic fibers (*J. Invest. Dermat.* **9**:17, 1947).

The present physical examination shows over the entire skin, except the palms and soles, ill-defined erythematous, slightly mottled granular plaques that look like spatters of dirty plaster of Paris. These areas are rough and composed of tiny hyperkeratotic follicular and papular prominences. Within such areas are several denuded spots and tiny blisters, and detachment of the epidermis can be easily elicited. In addition, there developed two years ago on the anterior part of the chest wall, lumbar region, and lower abdominal wall sharply demarcated lesions with an erythematous border and heavy silvery scales. The Auspitz phenomenon was present in all patches.

Histological examination showed hyperkeratosis, parakeratosis, and regular acanthosis; the portion over the rete covering the papillae was thin. In the corium, except for the perivascular lymphocytic infiltration, there was no obvious pathologic change. These features were typical of psoriasis.

Treatment consisted of both oral and parenteral administration of aureomycin, pregnenolone, and 100,000 units of vitamin A daily for several months, without any appreciable improvement. The psoriatic lesions, however, showed considerable regression following grenz-ray treatment (Dr. Hanfling). The dose applied to the scalp was 1,390 r, to the chest, 2,530 r, and to the sacrum, 3,600 r. The lesions, however, recurred three months after the cessation of the treatment.

DISCUSSION

DR. WILBERT SACHS: This case did not strike me as one of even atypical epidermolysis bullosa; I thought it was pemphigus.

DR. HENRY SILVER: The clinical picture warrants, in my opinion, the diagnosis of pemphigus erythematosus, since psoriasiform and bullous lesions and a Nikolsky sign are present.

DR. SAMUEL B. FRANK, Hartsdale: This patient's lesions show an unusual distribution for Hailey and Hailey dermatosis. A true Nikolsky sign can be elicited in this case.

DR. DAVID BLOOM: Clinically, the patient presents psoriasis in association with a bullous eruption which appears to be a benign type of pemphigus. It does not resemble the picture of Hailey and Hailey disease. Whether this association is coincidental or significant, I cannot say. About 20 years ago I reported a case in which psoriasis changed into pemphigus vulgaris; the patient died a few months later of the latter disease (*M. J. & Rec.* **130**:246 [Sept. 4] 1929).

DR. EARLE W. BRAUER (by invitation): On a number of occasions the patient was exposed to grenz rays, 240 to 300 r, with half-value layer of 28 microns Al, and he responded well in all areas exposed. However, recurrences did take place; the remissions were of several months' duration.

DR. CHARLES R. REIN: It would be interesting to do vital biopsies such as Dr. Frank and I reported on in this condition (ARCH. DERMAT. & SYPH. **45**:129-151 [Jan.] 1942).

DR. FREDERICK REISS: This patient was seen by various dermatologists 15 years ago; some considered the diagnosis of pemphigus foliaceus. Nine biopsies were performed on this man, all results pointing to this diagnosis. I do not believe that there is any doubt that the condition is generalized bullous dyskeratosis with the combination of psoriasis.

Lupus Miliaris Faciei. Presented by DR. JULIUS H. POLLOCK.

Hyperpigmentation. Presented by DR. NORMAN B. KANOF.

Case for Diagnosis: Pseudopelade (Brocq)? Presented by DR. HANS H. BIBERSTEIN.

Epidermolysis Bullosa Acquisita with Increased Coproporphyrin and Uroporphyrin. Presented by DR. JOHN GARB.

Tinea Capitis in Postpubertal Age Caused by Microsporum Audouini. Presented by DR. FREDERICK REISS.

Psoriasis Resembling Keratoderma of Haxthausen. Presented by DR. ABRAHAM J. ORFUSS.

Lichen Sclerosus et Atrophicus(?); Kraurosis Vulvae(?). Presented by DR. DAVID B. BALLIN.

Case for Diagnosis: Nevus? Presented by DR. LOUIS CHARGIN.

Tuberculoid Leprosy. Presented by DR. NATHAN SOBEL.

Lepromatous Leprosy. Presented by DR. FREDERICK REISS.

William Leifer, M.D., *President*

Henry Silver, M.D., *Secretary*

Oct. 18, 1951

Case for Diagnosis: Paget's Disease of the Scrotum? Presented by DR. FRANCES PASCHER, Brooklyn, and DR. CHARLES F. SIMS.

H. S. C., a man aged 43, was presented before this society at the March 16, 1950, meeting (A. M. A. ARCH. DERMAT. & SYPH. **63**:650-651, 1951), showing a well-defined eczematoid plaque on the right side of the scrotum and a similar lesion on the lateral aspect of the right ankle. Because of the histologic changes in the sections of the scrotal lesions, the diagnosis of Paget's disease (?) of the scrotum was entertained.

Histologic examination of a specimen taken from the lesion on the right ankle subsequently was reported as showing Bowen's disease. The lesion on the scrotum was excised in January, 1951, at the Kingsbridge Road Veterans Administration Hospital. The histologic diagnosis was erythroplasia of Queyrat. Slides of the excised lesion were forwarded to us upon request. The microscopic changes were interpreted here as those of carcinoma *in situ* in which Bowen-like changes predominated.

There is no evidence of a recurrence to date.

DISCUSSION

DR. PERRY M. SACHS: Actually, every case of Bowen's disease has some of the microscopic features of Paget's disease.

DR. FRANCES PASCHER, Brooklyn: From the clinical standpoint, in view of the lesion on the ankle and the unequivocal histologic changes noted in it, I am ready to represent this case as one of Bowen's disease of the scrotum and ankle. However, I should like to submit the views of the histopathologists who examined the sections. Dr. C. Sims originally diagnosed Paget's disease. Dr. Maurice N. Richter in a personal communication to us concurred in the diagnosis. The pathologists (personal communication) of the Kingsbridge Road Veterans Administration Hospital diagnosed the excised specimen as characteristic of erythroplasia (Queyrat). Dr. Hamilton Montgomery sent us an instructive and detailed report on the initial biopsy specimen. His report read as follows:

"The section that you sent me shows very definitely the features of a squamous-cell epithelioma *in situ* with individual cell keratinization, including giant mitoses and epithelial giant cells, the result of amitotic cell division, together with the other features that I have described for the group of precancerous dermatoses in which Bowen-like changes predominate. Vacuolation of epidermal cells is seen in arsenical epithelioma, and it might be well to inquire regarding ingestion of arsenic in this patient. The more I look at the section, however, the more I am convinced that there are also cells that fulfill all the requirements of the Paget cell. If we accept, therefore, that both Paget's disease and Bowen's disease are of epidermal origin, this becomes an exceptional case in which features of both conditions are definitely present in the same section and same lesion."

In view of the diverse interpretations of the histopathologic changes in this case it might be best to classify it as carcinoma *in situ* of the scrotum with histologic features of Paget's disease and Bowen's disease in the same lesion.

To his knowledge, the patient has never taken any medicine containing arsenic.

Case for Diagnosis: Congenital Cyst? Supernumerary Mamma? Presented by DR. JOHN GARB.

Y. L., a girl aged 15 years, was presented before this society at the March 16, 1950, meeting (A. M. A. ARCH. DERMAT. & SYPH. **63**:653, 1951), showing a mass in the neck of four and a half years' duration. Upon gross examination it appeared as a rounded, slightly fluctuant cyst-like lesion 8 cm. in diameter. There was a small ulcerating draining sinus over the center of the lesion.

She is presented again to show that there was no change in the cystic mass up to the time of the operation.

The cystic lesion was aspirated and sodium iodide injected for contrast studies with needle in place. A roentgenogram showed that it was localized and had no extension. Roentgen-ray study with iodized oil (lipiodol®) failed to reveal any extension of the dye beyond the cystic lesion itself.

A culture of material from the draining sinus was negative for acid-fast bacilli on Aug. 30, 1950. A roentgenogram of the chest showed no cardiac or pulmonary abnormality.

The mass was bluntly and sharply dissected out in its entirety on Oct. 9, 1951. Fibrous strands were not seen extending from the cyst wall. There was also no other evidence suggestive of a thyroglossal duct cyst.

The final diagnosis was cyst of the neck, compatible with pharyngothymic cyst.

Scleredema Adultorum (Buschke). Presented by DR. FRANCES PASCHER, Brooklyn, and DR. NORMAN B. KANOF.

M. S., a white man aged 80, was presented before this society at the Oct. 20, 1949, meeting (ARCH. DERMAT. & SYPH. **62**:760, 1950). In the summer of 1949 he first noticed a "hardness" around his neck, which quickly spread to involve the skin of the shoulders and the front and back of the chest. There was no history of any illness preceding the onset of the eruption.

The patient is presented again to show that the stiffness of the involved area has gradually resolved in part during the two years he has been under observation. It is roughly 50 to 75%

better than it was at the time of the original presentation. Most of the residual involvement is about the posterior aspect of the neck.

The patient received aureomycin by mouth, 0.25 gm. every four hours for two weeks and then 0.5 gm. four times a day for four weeks. Later he was given 1,200,000 units of penicillin intramuscularly over a three-week period. It was not felt that use of either drug altered the course of the condition.

DISCUSSION

DR. NORMAN B. KANOF: Since some of these cases have been reported to follow an infectious illness, the patient was treated with penicillin and aureomycin, but no benefits were observed from this therapy. In the two-year period he has been under observation, the patient has gradually improved.

DR. PERRY M. SACHS: When this case was first presented, I cited a case of my own, observed for one and a half years without evident improvement. I felt then that the condition often lasts much longer than the literature implies.

DR. WILLIAM LEIFER: In the literature there is a fair number of cases of this disease in which healing occurred only after many years. Two are cited by Epstein (ARCH. DERMAT. & SYPH. **37**:420, 1938) and one by Adler (*Zentralbl. Haut- u. Geschlechtskr.* **20**:259, 1926) in which edema of the eyelids was still present 30 years later. I saw a patient recently with edema of the upper cheeks and eyelids nine years after onset.

DR. CHARLES WOLF: Since the pathologic changes are in the collagen, it might be a fair assumption to institute cortisone treatment, particularly now that we have a slow-acting preparation. Perhaps small doses in this case would accelerate the involution.

DR. FRANCES PASCHER, Brooklyn: Two additional points may be made. This dermatosis appeared without any preceding illness, whereas the literature emphasizes the importance of upper respiratory infection as a forerunner of the disease. Second, as Dr. Leifer has already mentioned, it may last much longer than the year or two which is given as the average course in most dermatological texts. The scleredematous process in this case has been present more than two years and despite various forms of therapy, has shown little tendency to resolve.

Acrodermatitis Chronica Atrophicans Treated Successfully with Penicillin. Presented by DR. VICTOR H. WITTEN.

Acrodermatitis Chronica Atrophicans Treated with Penicillin. Presented by DR. VICTOR H. WITTEN.

DISCUSSION ON TWO PRECEDING CASES

DR. RAPHAEL BREAKSTONE: What is the rationale of the use of penicillin in these cases of acrodermatitis chronica atrophicans?

DR. FRANK E. CROSS: Whether the case is one of acrodermatitis chronica atrophicans or one of scleroderma matters not. What does matter is that the patient is benefited. For the first time we now have a remedy that is promising.

DR. ERNEST W. NATHAN: One patient in our service with typical acrodermatitis chronica atrophicans was treated with penicillin, and since then, over about a year and a half, it is interesting to note that from month to month the changes show regression. It would have been difficult for me to believe it had I not seen it myself.

DR. EMANUEL MUSKATBLIT: If we accept these cases as cases of acrodermatitis chronica atrophicans, then the most remarkable feature is the success of penicillin therapy. This is interesting not only from the point of view of therapeutic success but in its suggestion concerning the causation. The cause of this disease has so far been a mystery. If penicillin cures some of these patients, it speaks in favor of the disease being of infectious origin. One more point of interest is that if penicillin therapy can help in such late cases, its use certainly should be more valuable in the early stage before atrophy develops.

DR. JOHN GARB: In a discussion on scleroderma at the Skin and Cancer Unit many cases were cited of acrodermatitis chronica atrophicans treated with penicillin with good results.

On the other hand, I can cite two patients with the malignant type of scleroderma whose condition was not influenced by penicillin therapy. Another patient with scleroderma of the palms, arms, and legs showed no results after penicillin treatment for many months.

DR. IRWIN I. LUBOWE: Dr. Witten has treated a number of patients with acrodermatitis chronica atrophicans, and it would be of interest if he would tell us how successful he was in the cases not presented at this meeting. Several cases were reported of megaloblastic anemia in which treatment with penicillin alone was successful (*Brit. M. J.* **1**:380 [Feb. 24] 1951). We, therefore, observe that there may be some favorable, unexpected results from penicillin that are not due to its antibiotic action alone.

DR. CHARLES R. REIN: Dr. Hellerström has cited many patients throughout the Scandinavian countries who had acrodermatitis chronica atrophicans treated with penicillin; he stated that this is the most effective form of therapy.

DR. VICTOR H. WITTEN: The first report of the use of penicillin therapy in acrodermatitis chronica atrophicans came from Sweden, where Dr. Nanna Swartz originally treated two persons having the disease with considerable improvement. It was after Dr. Hellerström's report in this country on the patients of Nils Thyresson treated at the Karolinska Institute's Department of Dermatology that we obtained the details of treatment and started a small series of cases here. Thyresson treated 57 patients, of whom 11 showed only slight improvement and all the others excellent improvement. There were no failures in his series. Bianchi reported on the treatment of 17 patients, with excellent results in all. His series included a patient with lymphocytoma who also responded satisfactorily to penicillin therapy.

It is often difficult to make a clear-cut diagnosis when one must distinguish between the early infiltrative stages of scleroderma and acrodermatitis. Because of the often confused clinical picture, I feel that it is best to depend on the diagnosis of the histopathologist.

As would be expected, there was no improvement of existing atrophy in this series. There was usually rather prompt disappearance of the symptoms, which included itching, numbness, and/or pain. The infiltration gradually but regularly responded.

One can speculate on the mechanism of action of penicillin in this disease. At present it is thought that penicillin acts only as an antibiotic. If this is its only mode of action, then an infectious causation of the disease is most likely, whether it be a local involvement or secondary to organic or systemic involvement. Of course, it is possible that there are other actions of penicillin about which we are ignorant at present.

In all, six patients were treated. The condition in four was diagnosed as acrodermatitis chronica atrophicans by the dermatopathologist. No biopsies were done during or after treatment in my series. Three of these patients responded well and the fourth only slightly. A fifth patient, who clinically presented some of the features of acrodermatitis chronica atrophicans but did not show the characteristic histopathologic picture, failed to respond to treatment. The condition of the sixth patient, a physician seen with Dr. Sulzberger, was diagnosed clinically as acrodermatitis chronica atrophicans. A biopsy was not performed. The favorable response in this particular patient was dramatic.

Allergic Eczematous Contact-Type Dermatitis Due to Antiseptic in a Tooth Paste. Presented by DR. ALEXANDER A. FISHER, Woodside.

C. D., a woman aged 20, had been using "amm-i-dent" tooth paste for one year when first seen in June, 1951. Two months prior to this time there developed a dry, scaly dermatitis at the corners of the mouth which spread to the cheeks. On this account she was treated for a vitamin B deficiency, although there was no stomatitis or glossitis.

When she stopped using the "amm-i-dent" tooth paste, the eruption promptly cleared. On re-use of the "amm-i-dent" the eruption recurred.

Patch tests to "amm-i-dent" tooth paste and 5% "baxin" (the antiseptic in this dentifrice) in petrolatum gave positive reactions. Patch tests to other ammoniated tooth pastes, to the flavoring, and to other ingredients in "amm-i-dent" tooth paste showed negative results.

"Amm-i-dent" tooth powder and paste are unique among the ammoniated dentifrices in containing "baxin" (better known to the trade as G-4, which is dichlorodihydroxydiphenylmethane).

DISCUSSION

DR. ALEXANDER A. FISHER, Woodside: I recently had another patient, a young girl, with the same type of dermatitis due to the same dentifrice. I should like to ask that the floor be extended to Dr. Lipton, who is the patient recently described with stomatitis due to the dentifrice (A. M. A. ARCH. DERMAT. & SYPH. **64**:640, 1951).

DR. MAXWELL LIPTON (by invitation), Long Island City: The eruption began six months ago. My lips swelled; there was an area of tingling and burning with a cherry-red color. It was diagnosed as avitaminosis, and I was filled with plenty of vitamins. After two months I began to have pains in the ear and found it difficult to swallow. Finally I saw Dr. Fisher, who suggested the possibility of contact dermatitis due to the dentifrice. I stopped using it, and the condition cleared; I went back to using it, and it recurred. We decided the dermatitis was due to a certain component in the tooth paste.

DR. IRWIN I. LUBOWE: Dr. Fisher informs me that the allergenic agent responsible for the contact dermatitis is G-4, which is chemically closely related to G-11 (hexachlorophene). In view of the fact that hexachlorophene is being used widely by surgeons for preoperative asepsis, the dermatologist should be alert to sensitization from this product.

DR. WILLIAM LEIFER: I reported recently a case of contact dermatitis due to cinnamon (A. M. A. ARCH. DERMAT. & SYPH. **64**:52, 1951) but did not include in the paper the name of the tooth paste containing the cinnamon. The patient, a woman, had a dermatitis in the chin area, no stomatitis, and a chronic eczema of the hand of five years' duration. I tested her with the tooth-paste ingredients and found her sensitive only to the cinnamon. Incidentally, the chronic eczema of the hands also cleared when she stopped handling cinnamon.

DR. HERMAN SHARLIT: The implications in this case are important for the reason that hexachlorophene has a great vogue in industry. From what Dr. Fisher tells us, the incidence of sensitization must be relatively high if this single ingredient can affect all seven patients using the same product. This product is widely used in the Army against mildew in all sorts of fabrics, as well as in the manufacture of cosmetics. I think this should be followed up for safety.

DR. DAVID BLOOM: I had a patient with contact dermatitis apparently due to "pepsodent." Does Dr. Fisher know anything about this product?

DR. MORRIS LEIDER, Brooklyn: I have had two more cases of tooth-paste sensitivity, and "amm-i-dent" tooth paste was the culprit.

DR. ALEXANDER A. FISHER, Woodside: I must emphasize that while there are many ammoniated tooth pastes on the market only "amm-i-dent" has this antiseptic. It is known in the trade as G-4. I patch-tested the patients with the "amm-i-dent" itself and with all its ingredients, including G-4 (5% of the suspension in petroleum jelly), cinnamon, and essential oil; none reacted to any ingredient except the G-4. All four patients reacted to it. I have not had any experience with "pepsodent," which so far as I know does not contain this antiseptic.

Case for Diagnosis: Atypical Granuloma Annulare? Necrobiosis Lipoidica Diabeticorum? (Left Wrist, Right Ankle); Inflammatory Plaques with Secondary Atrophy? (Back). Presented by DR. FRANCES PASCHER, Brooklyn, and DR. CHARLES F. SIMS.

Bullosis Actinica et Mechanica (Brunsting-Mason). Presented by DR. JOHN GARB.

Amyloidosis. Presented by DR. DAVID B. BALLIN.

Case for Diagnosis: Exudative Discoid and Lichenoid Dermatitis? Mycosis Fungoides? Presented by DR. JULIUS H. POLLOCK.

Morphea. Presented by DR. DAVID BLOOM.

Lichen Sclerosus et Atrophicus. Presented by DR. IRWIN I. LUBOWE.

News and Comment

ANNOUNCEMENTS

Annual Prize Essay Contest of The American Dermatological Association, Inc.—The winners of the second annual essay contest of the American Dermatological Association were as follows: First prize, Paul D. Rosahn, M.D., New Britain, Conn., "The Adverse Influence of Syphilitic Infection on the Longevity of Mice and Men," and honorable mention, Peter Flesch, M.D., Philadelphia, "Hair Loss from Sebum." Dr. Rosahn received the cash award and presented his paper at the meeting of the Association at the Broadmoor Hotel, Colorado Springs, Colo., April 23, 1952.

The American Dermatological Association is again offering a prize of $300 for the best essay submitted for original work, not previously published, relative to some fundamental aspect of dermatology or syphilology. The purpose of this contest is to stimulate investigators to original work in these fields.

Manuscripts typed in English with double spacing and ample margins, as for publication, together with illustrations, charts, and tables, all of which must be in triplicate, are to be submitted not later than Jan. 1, 1953. The manuscripts should be sent to Dr. Louis A. Brunsting, Secretary, American Dermatological Association, Inc., 102-110 Second Ave., S. W., Rochester, Minn. Those which are incomplete in any of the above respects will not be considered.

Competition in this prize contest is open to scientists generally, not necessarily to physicians alone.

The award will be made by a committee of judges selected to pass on the essays by the Research Aid Committee of the American Dermatological Association, and the decision of the judges shall be final. The essays are judged on the following considerations: (1) originality of ideas, (2) potential importance of the work, (3) experimental methods and use of controls, (4) evaluation of results, and (5) clarity of presentation. This contest is planned as an annual one, but if in any year, at the discretion of the committee and judges, no paper worthy of a prize is offered, the award may be omitted.

The prize-winning candidate may be invited to present his paper before the annual meeting of the American Dermatological Association with expenses paid in addition to the $300 prize. Further information regarding this essay contest may be obtained by writing to the secretary of the American Dermatological Association.

The next annual meeting of the American Dermatological Association, Inc., will be held June 9 to 13, 1953, at The Lake Placid Club, Essex County, New York.

GENERAL NEWS

Specialists Certified by the American Board of Dermatology and Syphilology.—At its meeting in Chicago on May 8, 1952, the American Board of Dermatology and Syphilology certified the following physicians: Theodore D. Arlook, Elkhart, Ind.; Norman D. Asel, Camp Carson, Colo.; Seth S. Barnes, Cape Girardeau, Mo.; Carl Z. Berry, Drexel Hill, Pa.; Donald J. Birmingham, Cincinnati; Frederick H. Chard, Wichita, Kan.; Morris M. Cohen, Baltimore; John H. Cox, Drexel Hill, Pa.; Paul M. Crossland, Santa Rosa, Calif.; William M. Enright, San Diego, Calif.; William E. Flood, Fort Worth, Texas; Jerome M. Greenhouse, Clayton, Mo.; Edward J. Jones Jr., Youngstown, Ohio; Carl V. Kaess, Jacksonville, N. C.; Andrew Kallos, New York; Irvine M. Karon, St. Paul; Louis Keller, Clayton, Mo.; Henry H. Klein, Brooklyn; Leonard Klein, Rego Park, N. Y.; William C. Miller, Wausau, Wis.; Hilbert M. Mueller, South Bend, Ind.; Samuel M. Perlstein, Philadelphia; Van Rensselaer Richmond, Fort Benning, Ga.; John B. Roxby Jr., Philadelphia; Jonas E. Schreider, Walnut Creek, Calif.; William Snyder, Paterson, N. J.; Elliot A. Wallach, Richmond Heights, Mo.; Jack Weiner, Philadelphia; Richter H. Wiggall, Knoxville, Tenn., and Frank G. Witherspoon, Nashville, Tenn.

As of July 1, 1952, the following physicians were certified: Lester J. Bienvenu, Manchester, N. H., and Lydia C. Marshak, Aurora, Ill.

The following dermatologists also passed the examinations and will be certified upon completion of other requirements: David Bacharach, Baltimore; Clinton G. Beirne and Gilbert A. Beirne, San Francisco; Hoyt C. Blaylock, Wichita, Kan.; Earl W. Brauer, West Englewood, N. J.; Harold H. Bremers, Omaha; James W. Bringe, Sheboygan, Wis.; William J. Campbell, Harrisburg, Pa.; Kathleen S. Cawthon, New York; Joseph T. Chiaramonte, Brooklyn; Paul V. Chivington Jr., Cleveland; Sidney G. Clyman, New York; Walter J. Cole, Los Altos, Calif.; Kenneth G. Colling, London, Ont., Canada; Porter F. Crawford, Durham, N. C.; John T. Crissey, Philadelphia; Robert L. Day, Bakersfield, Calif.; Cleveland R. Denton, Burlington, Vt.; Helen L. T. Dexter, Cincinnati; John W. Didcoct, Urbana, Ill.; Calvin J. Dillaha, Little Rock, Ark.; Mitchell Ede, Rochester, Minn.; Seymour Fried, New York; Asher A. Friedman, Norfolk, Va.; John E. German, Reading, Pa.; Gordon E. Gifford, Zanesville, Ohio; Arthur H. Gladstein, Astoria, N. Y.; Harold Glick, New York; Raymond W. Goldblum, Pittsburgh; Norman J. Goldfarb, Forest Hills, N. Y.; Marvin S. Greenberg, Philadelphia; George W. Hambrick Jr., Princeton, W. Va.; Everett R. Harrell Jr., Ann Arbor, Mich.; Ralph Keen, Jamaica, N. Y.; John J. Laskas, Springfield, Pa.; John T. Latham, Greenville, S. C.; John E. LeDonne, Revere, Mass.; Aaron B. Lerner, Ann Arbor, Mich.; Carl S. Lingamfelter, Richmond, Va.; Dorothy R. Lynn, Philadelphia; Ansel R. Martin, Jamestown, N. Y.; Theodore J. Michelfelder, New York; George H. Mitchell, Philadelphia; Jonas F. Mullins, Brownwood, Texas; Harold O. Perry, Rochester, Minn.; Nils T. Peterson, El Segundo, Calif.; George L. Popkin, Roosevelt, Long Island, N. Y.; Hugh B. Praytor, Trussville, Ala.; Milton Reisch, New York; Charles Reiter Jr., Port Arthur, Texas; Evelyn M. Rockwell, Milford, Ohio; Sidney I. Rogers, Brooklyn; Edwin R. Rushkin, New Rochelle, N. Y.; Eugene P. Schoch Jr., Austin, Texas; Raymond R. Simpson, Alton, Ill.; Kenneth A. Smith, Nanticoke, Pa.; Stuart C. Smith, Portsmouth, Va.; Rufus A. Stevenson Jr., Temple, Texas; Ralph Teicher, Brooklyn; Ernest R. Trice, Richmond, Va.; Eugene J. Van Scott, Macedon, N. Y.; Harry Van Velsor, Troy, N. Y.; John B. Watson, Hollywood, Calif.; William W. Wells, Schenectady, N. Y.; Edward S. Wikiera, Detroit; Alexander W. Young Jr., Wheeeling, W. Va., and Abraham Zelony, Brooklyn.

Directory of Dermatologic Societies *

INTERNATIONAL

Sir Archibald Gray, President, 39 Devonshire Place, London, W. 1.
R. M. B. MacKenna, Academic Secretary, St. John's Hospital for Diseases of the Skin, Lisle St., Leicester Sq., London, W. C. 2.
Place: London, England. Time: July 21-26, 1952.

FOREIGN

Canadian Dermatological Association

E. Gaumond, President, 34 rue de la Fabrique, Quebec.
S. E. Grimes, Secretary, 404 Medical Arts Bldg., Ottawa.
Place: Seigniory Club, Montebello, Quebec.

German Society of Dermatology

Alfred Marchionini, Chairman, Dermatological Clinic, University of München.
Otto Grütz, Secretary, Dermatological Clinic, University of Bonn.

Israeli Dermatological Society

A. Dostrovsky, Chairman, Hebrew University Hadassah Medical School, Jerusalem.
Felix Sagher, Secretary, Hebrew University Hadassah Medical School, Jerusalem.

New Zealand Dermatological Society

P. E. Allison, President, 137 Cambridge Tce., "Harley," Christchurch.
R. G. Park, Secretary, Kelvin Chambers, 16 The Terrace, Wellington, C. I.

N. S. W. Branch of British Association of Dermatology and Syphilology

F. C. Thompson, President, 141 Macquarie St., Sydney.
A. Geoffrey Finley, Secretary, 234 Macquarie St., Sydney.
Place: Royal Prince Alfred Hospital, St. Vincent's Hospital, Royal North Shore Hospital, Lewisham Hospital, Royal Alexandra Hospital for Children, Sydney Hospital, and Royal Newcastle Hospital, in rotation. Time: 4:00 p. m., on Fridays, approximately every two months.

North British Dermatological Society

President: Senior dermatologist in city where meeting is held.
P. W. Hannay, Honorary Secretary, 22 Nile Grove, Edinburgh, 10.

Royal Academy of Medicine in Ireland, Section of Dermatology

M. Drummond, President, 22, Upper Fitzwilliam St., Dublin.
B. Solomons Jr., Secretary, 42, Fitzwilliam Sq., Dublin.
Place: Royal College of Physicians of Ireland. Time: Approximately every two months.

Royal Society of Medicine, Section of Dermatology

G. B. Dowling, President, 24, Wimpole St., London, W. 1.
D. I. Williams and H. E. Vickers, Secretaries, 1, Wimpole St., London, W. 1.
Place: Royal Society of Medicine, 1 Wimpole St., London, W. 1. Time: 4:00 p. m., third Thursday of each month.

Sociedade Brasileira de Dermatologia e Sifilografia

Demétrio Peryassú, President.
Luiz Campos Melo, Secretary, Caixa postal 389, Rio de Janeiro.
Place: Rio de Janeiro. Time: Last Wednesday of each month.

*Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date. The directory will be published in each July issue.

Sociedad Mexicana de Dermatologia

Silvestre Rico, Chairman.
Fernando Latapi, Secretary, Zacatecas 220-6, México, D. F.
Place: National School of Medicine, México, D. F. Time: 9:00 p. m., first Thursday of each month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

John H. Lamb, Chairman, 705 Medical Arts Bldg., Oklahoma City 2.
J. Walter Wilson, Secretary, 3875 Wilshire Blvd., Los Angeles 5.
Place: New York. Time: June 1-5, 1953.

American Academy of Dermatology and Syphilology

C. Guy Lane, President, 416 Marlborough St., Boston 15.
John E. Rauschkolb, Secretary, 25 Prospect Ave., N. W., Cleveland 15.
Place: Palmer House, Chicago. Time: Dec. 6-11, 1952; Dec. 5-10, 1953.

American Board of Dermatology and Syphilology, Inc.

Donald M. Pillsbury, President, 133 S. 36th St., Philadelphia 4.
George M. Lewis, Secretary, 66 E. 66th St., New York 21.

American Dermatological Association

Earl D. Osborne, President, 71 North St., Buffalo 2.
Louis A. Brunsting, Secretary, 102 Second Ave. S.W., Rochester, Minn.
Place: The Lake Placid Club, Essex County, New York. Time: June 9-13, 1953.

Society for Investigative Dermatology

Theodore Cornbleet, President, 30 N. Michigan Ave., Chicago 2.
Herman Beerman, Secretary, 255 S. 17th St., Philadelphia 3.
Place: New York. Time: June, 1953.

SECTIONAL

Central States Dermatological Association

Harold N. Cole, President, 1422 Euclid Ave., Cleveland 15.
Roy H. Holmes, Secretary, 289 W. Western Ave., Muskegon, Mich.

New England Dermatological Society

Joseph Goodman, Secretary, 375 Commonwealth Ave., Boston.
Place: New Haven Hospital, New Haven, Conn., and Massachusetts General and Boston City hospitals (in alternation), Boston.

Northern New Jersey Dermatological Society

Eva T. Brodkin, President, 365 Osborne Terrace, Newark.
F. C. Licks, Secretary, 64 Scotland Rd., South Orange.
Place: Academy of Medicine, Newark. Time: 8:00 p. m., second Tuesday in October, November, January, March, and May.

Pacific Dermatological Association

Nelson P. Anderson, President, 2007 Wilshire Blvd., Los Angeles.
Ervin Epstein, Secretary, 447 29th St., Oakland, Calif.

Pacific Northwest Dermatological Society

Sam E. Light, President, Medical Arts Bldg., Tacoma, Wash.
Leon F. Ray, Secretary, 628 Medical Dental Bldg., Portland 5, Ore.
Place: Place varies. Time: Third Thursday of May and October.

Rocky Mountain Dermatologic Society

G. P. Lingenfelter, President, 910 Republic Bldg., Denver.
David J. Musman, Secretary, 1024 Republic Bldg., Denver.
Place: Selected prior to each meeting. Time: Selected prior to each meeting.

Southeastern Dermatological Association

Richard W. Fowlkes, President, 701 Professional Bldg., Richmond 19, Va.
Robert N. Buchanan Jr., Secretary-Treasurer, 326 Doctors Bldg., Nashville, Tenn.
Time: September, 1952.

Southern Medical Association, Section on Dermatology and Syphilology

D. Truett Gandy, President, 424 Medical Arts Bldg., Houston 2, Texas.
Ray O. Noojin, Secretary, 620 S. 20th St., Birmingham, Ala.
Place: Miami, Fla. Time: Nov. 10-13, 1952.

Southwestern Dermatological Society

Leslie M. Smith, President, First National Bank Bldg., El Paso, Texas.
George K. Rogers, Secretary, Lois Grunow Memorial, Phoenix, Ariz.

STATE

Alabama Dermatological Society

Ray J. Noojin, President, 620 S. 20th St., Birmingham.
James S. Snow, Secretary, First National Bank Bldg., Tuscaloosa.
Time: Fourth Monday of each month, September to May.

Arkansas Dermatological Society

Davis W. Goldstein, Chairman, Cooper Clinic, Fort Smith.
Ray Fulmer, Secretary, 103 E. Seventh St., Little Rock.

California Medical Association, Scientific Assembly, Dermatology and Syphilology Section

Rees B. Rees, Chairman, 380 Post St., San Francisco.
Frances M. Keddie, Secretary, 300 Homer Ave., Palo Alto.

Connecticut State Medical Society, Section on Dermatology

Joseph Becker, Chairman, 302 State St., New London.
Jack J. Albom, Secretary, 43 Trumbull St., New Haven.
Place: New Haven.

Florida Society of Dermatology and Syphilology

Lewis Capland, President, 350 Lincoln Rd., Miami Beach 1.
Morris Waisman, Secretary, 1201 Citizens Bldg., Tampa 2.

Hawaii Dermatological Society

Harry L. Arnold Jr., Secretary, 881 S. Hotel St., Honolulu 53.
Place: 881 S. Hotel St., Honolulu. Time: Every three months when possible.

Indiana State Dermatological Society

Daniel Tweedal, President, 527 Sycamore St., Evansville.
Robert E. Jenkins, Secretary, 3311 N. Meridian, Indianapolis 8.

Louisiana Dermatologic Society

Leslie K. Mundt, Chairman, 3508 Coliseum St., New Orleans.
W. Kohlmann Reed, Secretary, 607 Maison Blanche Bldg., New Orleans.
Place: Charity Hospital, New Orleans. Time: Third Sunday of each month.

Massachusetts Medical Society, Section on Dermatology and Syphilology

Ethel M. Rockwood, President, 416 Marlborough St., Boston 15.
S. J. Messina, Secretary, 520 Commonwealth Ave., Boston 15.
Place: Hotel Statler, Boston.

Medical Society of the State of New York, Section on Dermatology and Syphilology

George M. Lewis, President, 66 E. 66th St., New York 21.
Frank A. Dolce, Secretary, 468 Delaware Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON DERMATOLOGY

Herman Beerman, President, 255 S. 17th St., Philadelphia.
Thomas Butterworth, Secretary, 411 Walnut St., Reading.

MICHIGAN STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

J. R. Delaney, Chairman, 1020 David Whitney Bldg., Detroit 26.
C. J. Courville, Secretary, 1202 Maccabees Bldg., Detroit 2.

MINNESOTA DERMATOLOGICAL SOCIETY

Elmer T. Ceder, President, 511 Medical Arts Bldg., Minneapolis 2.
Harold G. Ravits, Secretary, 546 Lowry Medical Arts Bldg., St. Paul.

OKLAHOMA DERMATOLOGICAL SOCIETY

Phyllis F. Jones, President, 705 Medical Arts Bldg., Oklahoma City 2.
C. P. Bondurant, Secretary, 412 Medical Arts Bldg., Oklahoma City 2.
Place: Oklahoma City and Tulsa, alternately. Time: Annually, in the spring.

RHODE ISLAND DERMATOLOGICAL SOCIETY

William B. Cohen, President, 105 Waterman St., Providence 6.
Bencel L. Schiff, Secretary, 251 Broadway, Pawtucket.
Time: Second of November, January, and March, each year.

TEXAS DERMATOLOGICAL SOCIETY

C. H. McCuistion, President, 609 Capital National Bank Bldg., Austin.
Thomas L. Shields, Secretary, 1216 Pennsylvania Ave., Fort Worth.
Place: Rotating. Time: Spring, coincident with Texas State Medical Association; fall, October.

LOCAL

BALTIMORE-WASHINGTON DERMATOLOGICAL SOCIETY

Frederick Glass, President, 833 Park Ave., Baltimore 1.
Jack L. Derzavis, Secretary, 1835 Eye St., N. W., Washington, D. C.
Place: Baltimore and Washington. Time: Third Thursday of each month in alternate cities, October to May.

BRONX DERMATOLOGICAL SOCIETY

Charles R. Rein, President, 580 Fifth Ave., New York.
Henry Silver, Secretary, 290 West End Ave., New York.
Place: Academy of Medicine. Time: Third Thursday of every month, October to May.

BROOKLYN DERMATOLOGICAL SOCIETY

Moses Silverman, President, 466 Bay Ridge Pkwy.
C. B. Locasto, Secretary, 567 First St. (15).
Place: Brooklyn Hospital Clinic, Ashland Place and De Kalb Ave. Time: 8:30 p. m., third Monday of each month, October to June.

BUFFALO-ROCHESTER DERMATOLOGICAL SOCIETY

Marvin Winer, President, 333 Linwood Ave., Buffalo.
Frank A. Dolce, Secretary, 468 Delaware Ave., Buffalo.
Place: Edward J. Meyer Memorial Hospital, Buffalo, and Strong Memorial Hospital, Rochester. Time: Second Tuesday of every month, October to May, inclusive.

CENTRAL NEW YORK DERMATOLOGICAL SOCIETY

Joseph J. Russo, President, 736 Madison Ave., Albany.
Frank Fagan, Secretary, 65 2d St., Troy.

CHICAGO DERMATOLOGICAL SOCIETY

Theodore Cornbleet, President, 1819 W. Polk St. (12).
Irene A. Neuhauser, Secretary, 7 W. Madison St. (2).
Place: Chicago. Time: Third Wednesday of each month except June, July, August, and September.

Cincinnati Society of Dermatology and Syphilology

Harry A. Nieman, President, 570 Fidelity Bldg., Dayton, Ohio.
Raymond R. Suskind, Secretary, Kettering Laboratory, University of Cincinnati, Cincinnati.
Place: Cincinnati General Hospital. Time: 8:00 p. m., first Wednesday of each month, October to May.

Cleveland Dermatological Society

George H. Curtis, President, Cleveland Clinic (6).
John R. Haserick, Secretary, Cleveland Clinic (6).

Dallas Dermatological Society

Bedford Shelmire, President, 1410 Medical Arts Bldg.
D. Shelton Blair, Secretary, 304 Medical Arts Bldg.
Place: Medical Arts Bldg. Time: Third Wednesday of each month.

Detroit Dermatological Society

Chester A. Doty, President, 1735 David Whitney Bldg. (26).
Henry A. Brunsting, President-Elect, 2001 Collingwood Ave., Toledo, Ohio.
Charles J. Courville, Secretary, 1202 Maccabees Bldg. (2).
Place: Local hospitals in Detroit and vicinity. Time: Third Tuesday of each month except June, July, August, and September.

Kansas City Dermatological Society

Thomas B. Hall, President, 902 Professional Bldg., Kansas City 6, Mo.
Bernard H. Winston, Secretary, 324 Professional Bldg., Kansas City 6, Mo.
Place: University of Kansas Medical Center, Kansas City, Kan. Time: 10:00 a. m., second Sunday of each month, from October through June.

Long Island Dermatologic Society

Ida J. Mintzer, President, 88-50 163d St., Jamaica 3, N. Y.
Conrad Stritzler, Secretary, 90-26 148th St., Jamaica 2, N. Y.

Los Angeles Dermatological Society

Walter Schwartz, President, 696 E. Colorado Blvd., Pasadena, Calif.
J. Walter Wilson, Secretary, 3875 Wilshire Blvd., Los Angeles.
Place: Good Hope Clinical Association. Time: Second Tuesday of each month, October to May.

Manhattan Dermatologic Society

Samuel Peck, President, 33 E. 70th St. (21).
George M. Lewis, Secretary, 66 E. 66th St. (21).
Place: Each member's office, in rotation. Time: 8:00 p. m., second Tuesday of each month.

Metropolitan Dermatological Society

Joseph C. Amersbach, President, 105 E. 53d St., New York.
Valentine C. Baker, Secretary, 619 W. 140th St., New York.
Place: Offices of members. Time: Third Monday of each month, October to May.

Metropolitan Dermatological Society of Chicago

I. M. Cobin, President, 108 Scott St., Joliet, Ill.
Tibor Benedek, Secretary, 25 E. Washington St. (2).
Place: Chicago, alternating in the Services of the Fellows. Time: Second Wednesday, 10:00 a. m., from October through May.

Metropolitan Dermatological Society of Los Angeles

Harold C. Fishman, President, 105 N. San Vicente Blvd., Beverly Hills, Calif.
Fred F. Feldman, Secretary, 6333 Wilshire Blvd., Los Angeles.
Place: Good Hope Clinic, Los Angeles. Time: Fourth Tuesday of each month, October through May.

Montreal Dermatological Society

Georges Leclerc, President, 418 Sherbrooke St. E.
R. Roy Forsey, Secretary, 1414 Drummond St.
Place: Royal Victoria Hospital, Notre Dame Hospital, Montreal General Hospital, and other hospitals. Time: October, February, and April.

New York Academy of Medicine, Section of Dermatology and Syphilis

Anthony C. Cipollaro, President, 40 E. 61st St. (21).
J. Lowry Miller, Secretary, 371 Park Ave.
Place: New York Academy of Medicine, 2 E. 103d St. Time: First Tuesday of each month.

New York Dermatological Society

Anthony C. Cipollaro, Chairman, 40 E. 61st St. (21).
Maurice J. Costello, Secretary, 140 E. 54th St.
Place: New York. Time: Fourth Tuesday of each month.

Omaha Dermatological Society

Olin J. Cameron, 1520 Medical Arts Bldg.
George F. Pinne, Secretary, 453 Aquila Ct.
Time: Third Wednesday of each month, September to June.

Philadelphia Dermatological Society

Frederick D. Weidman, Chairman, University of Pennsylvania School of Medicine (4).
Bertram Shaffer, Secretary, 1825 Pine St. (3).
Place: Philadelphia hospitals. Time: Third Friday of each month except June, July, and August.

Pittsburgh Dermatological Society

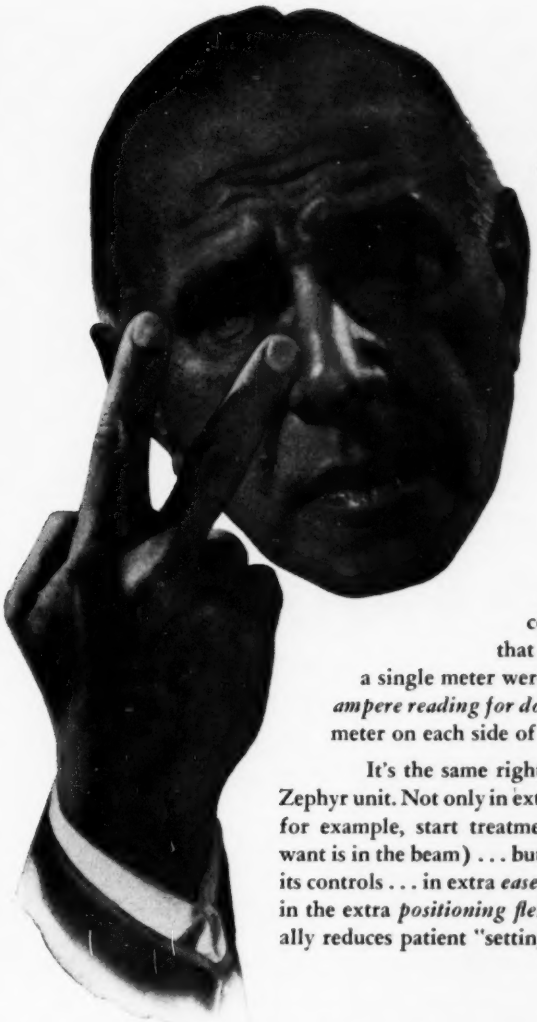
Paul V. Graham, President, 1300 Market St., Wheeling, W. Va.
S. R. Perrin, Secretary, 906 Highland Bldg., Pittsburgh 6.
Place: Falk Clinic, 3601 Fifth Ave. Time: Evening of third Thursday of each month except July and August.

San Francisco Dermatological Society

Rees B. Rees, President, 384 Post St.
Max Krause, Secretary, 400 59th St., Oakland 9, Calif.

St. Louis Dermatological Society

Joseph Grindon Jr., President, 539 N. Grand Ave. (3).
Morris Moore, Secretary, 3427 Washington Blvd.
Place: Barnard Free Skin and Cancer Hospital. Time: 8:00 p. m., third Monday of each month, October to May.



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Archives of Dermatology and Syphilology, February, 1949: 243-245
Abdominal Surgery, Bancroft and Wade, 1947: 804

ECZEMAS of the EAR

Archives of Otolaryngology, March, 1947: 294-297
Bulletin of the Johns Hopkins Hospital, Sept., 1948: 225-228
The Eye, Ear, Nose and Throat Monthly, April, 1950: 200-203

DERMATOMYCOSIS of the HANDS and FEET

Southern Medical Journal, January, 1951: 42-44

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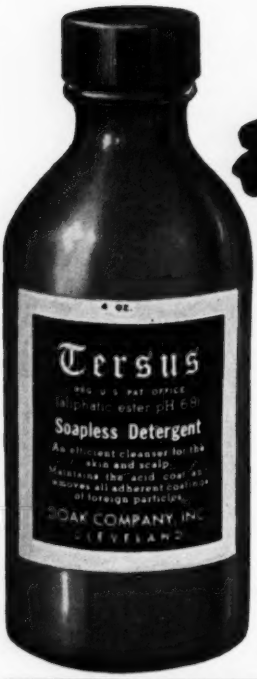

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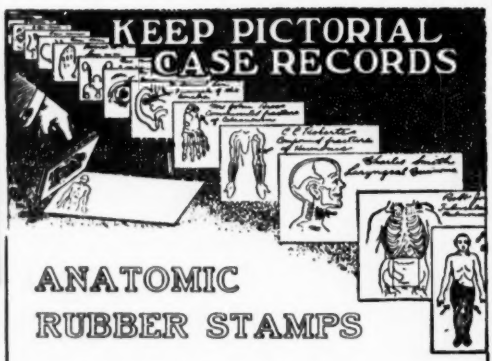

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Now, however, the Toni Company puts custom-made permanents within the budget of every woman. The new Toni Trio lets the woman choose from 3 permanents—the one just right for her type of hair. *Regular* Toni for normal hair. *Super* Toni for hard-to-wave hair. *Very Gentle* Toni for easy-to-wave hair.

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for normal hair

SUPER TONI
for hard-to-wave hair

VERY GENTLE TONI
for easy-to-wave hair

IMPORTANT TO DOCTORS

The waving lotion for each of these permanents has been formulated with the scientific precision that characterizes the research on all Toni products. The dermatological safety of these formulae was confirmed by a period of comprehensive testing. These pre-marketing tests included patch tests and controlled half-head tests; toxicity tests on animals; chemical and physical examination of off-the-head tresses; and use by thousands of women in market tests. The results all provide consistent evidence of product safety.

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What It Is For . . .

CROLEUM Vehicle is an excellent base in which to compound prescribed topical drugs. Pour desired quantity of CROLEUM Vehicle into glass or porcelain mortar and blend in the prescribed medications with pestle (non-metallic). CROLEUM Vehicle will dissolve aqueous or oil soluble drugs. Insoluble drugs or amounts in excess of saturation level will remain suspended in the carrier over wide temperature variations.

CROLEUM Vehicle without added medication is an excellent non-irritating, low cost, dermal emollient and detergent. It finds many hospital uses as an effective massage lubricant, skin cleanser and general purpose skin lotion. Dilute with distilled water if thinner consistency is desired.

How Administered . . .

CROLEUM is non-drying and flows readily. Apply to skin with spray, swab or sponge—flow it on—spread with sterile tongue blade—or dilute with sterile distilled water (50%) and spray. Use also as a wet dressing or pack. Dressings will seldom adhere to CROLEUM treated surfaces.

What It Does . . .

While this is determined by the added medicament and its strength, CROLEUM prepared prescriptions of low drug concentration may produce therapeutic results not surpassed by larger amounts in ordinary grease bases. No grease films are formed. CROLEUM with added medication actively penetrates incrustations and small dermal crevices and thus provides intimate medication contact in otherwise inaccessible places.

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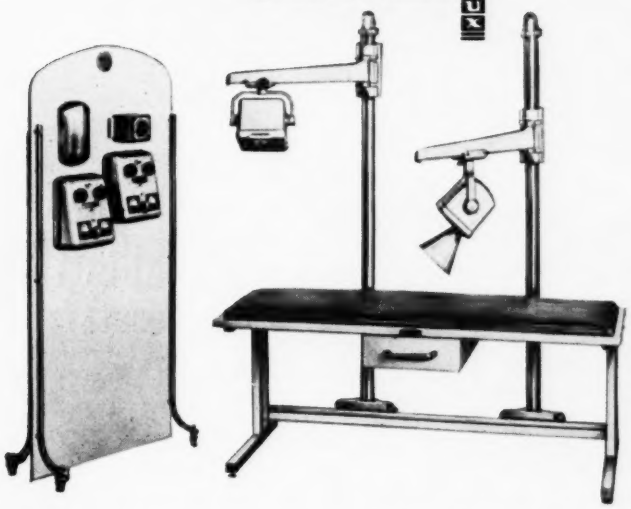

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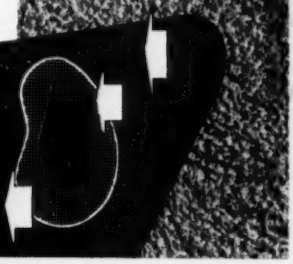

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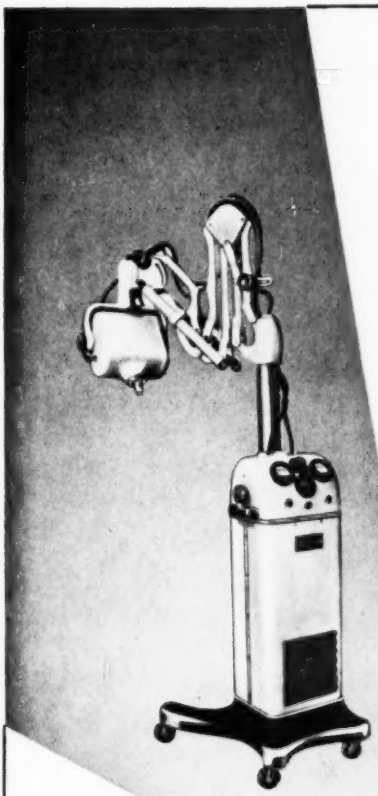

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